estimated at US $ 0.1 per dose, may be attractive for some manufacturers. Thus, the WHO Global Action Plan thus encourages increased production and technology transfer of LAIV.

The use of specific pathogen free (SPF) embryonated chicken eggs is not a regulatory requirement for the production of LAIV. One country has produced LAIV in non-SPF eggs for 50 years. More recently in another country, one manufacturer chose to use SPF eggs for its production of seasonal LAIV. If SPF eggs were chosen for pandemic influenza vaccine production the egg supply will most likely be insufficient if not at all achievable under a pandemic situation. Therefore, the use of non-SPF eggs and cell-culture need to be considered for the production of pandemic LAIV.

Unresolved potential public and animal health concerns are associated with live attenuated vaccines for novel 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 been used extensively in the past:

- 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*). Most countries however 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 (*5*) in immunologically naïve individuals (e.g. small children and persons with no contact to circulating influenza viruses). Individuals with residual immunity display a booster rather than a primary immunization effect after 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 strains.

All seasonal inactivated influenza vaccines are formulated to meet the WHO Requirements of not less than 15 ug of haemagglutinin per serotype 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 seasonal inactivated influenza vaccines. Currently used continuous cell lines include Vero cells which are widely used in

manufacturing of other vaccines, the MDCK cell line and others which are less extensively used as a human vaccine substrate.

Further, 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. Interestingly, 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 study on protection against heterologous virus and minor variants as well as evidence of herd immunity induction through childhood vaccination is 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 pandemic human influenza vaccines

B.1 General remarks

To ensure timely supply of human pandemic influenza vaccines, stringent time requirements will have to be met for identification of vaccine candidate strains, preparation of seed lots, testing and licensing as well as manufacturing and distribution. Based on current experience and technologies, manufacturers require approximately three months from seed strain availability to release of first lot of vaccine for testing. Delays in the production of pandemic vaccine seed strains may occur, as highlighted by technical difficulties encountered in trying to produce a vaccine against the H5N1 virus involved in the 2003 H5N1 outbreak in Asia.

The purpose of this section of the document is to:

- describe possible regulatory pathways to be considered by NRAs in licensing human pandemic influenza vaccines
- identify existing regulatory methods in the licensing process of human pandemic influenza vaccines
- deliniate regulatory areas with potential for international harmonization.

B.2 Establishing a regulatory pathway

The regulatory processes for human 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 vaccine for use in a pandemic situation. Emergency options have also been identified should a pandemic 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 human pandemic influenza vaccines of the five 5 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, if warranted and possible, changes to regulations or pursue mechanisms to obtain or use additional regulatory authority in an emergency situation.

B.2.1. Commonalities of five selected National Regulatory Authority pathways

The five NRAs studied have the following in common, or near in common, with respect to the licensure of a human 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 annual influenza vaccine(s);
- All have inspectorate qualified to conduct Good Manufacturing Practices (GMP) inspections, most using the Pharmaceutical Inspection Cooperation Scheme (PIC/S)
- Note: The United States recently applied and Japan is not a member of PIC/S;
- All have outlined regulatory pathways for the licensing of human 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 a pandemic 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 for 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 a pandemic;
- All have identified emergency use options and provisions, including evaluating potential risks and benefits should a pandemic 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 influenza vaccine regulatory pathways presented in this document is to only provide information to NRAs and manufacturers and should not be taken as any sort of WHO endorsement of any specific regulatory pathway.

Europe, the United States, Australia and Japan plan to license inactivated vaccines for novel influenza viruses. Canada will require data from a vaccine for a novel influenza virus to license the pandemic but has no current plans to license vaccines for novel influenza viruses itself.

Within the European context, there are two regulatory pathways that can be followed depending on the intended use of a vaccine for a novel influenza virus. In one scenario, the vaccine for a novel influenza virus although licensed, is not intended to be used or marketed before the pandemic is announced and the exactly matching pandemic strain has to be introduced into the authorization via a fast track type two variation. In the second scenario, where a vaccine for a novel influenza virus is intended to be used before the pandemic is declared, then special regulatory provisions apply (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 influenza viruses is limited to inactivated vaccines. No guidance exists for LAIV.

Currently in the USA, all submissions for the initial licensure of vaccine for novel influenza viruses or a pandemic influenza vaccine would be submitted as a Biologics License Application (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.

Japan's approval of vaccines for novel influenza viruses is intended to support the subsequent approval of the pandemic vaccine, but if the strain in a vaccine for a novel influenza virus and the pandemic virus strain are similar, the approval for the vaccine for novel human influenza virus could be considered a market authorization for the pandemic vaccine.

Canada has entered into a contract with one domestic supplier to provide enough pandemic vaccine for the entire Canadian population; therefore, regulatory preparedness is based on the concept of a single supplier. Australia, Japan, US, and the EMEA's regulatory preparedness are based on multiple suppliers. Pandemic vaccine manufacturing in Japan will rely heavily on three not-for-profit entities and a commercial manufacturer (The Japanese government does not distinguish between public and private manufacturing entities).

Europe and the US have numerous guidance documents for vaccines. Australia references many EU and US guidance documents and Canada has recently developed a guidance document for pandemic vaccine manufacturers. Japan has published a policy document on the H5N1 vaccine regulatory process. In May 2007, the US released 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.

B.3 Towards a harmonized regulatory pathway

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

- the availability of human pandemic influenza vaccine in a timely manner at global scale;
- WHO pre-qualification of human pandemic influenza vaccines; and
- the ability to distribute pandemic influenza vaccine between countries. However, transfer of seed strains, particularly wild type 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 preparedness plans and all countries will be constrained somewhat by the existing laws and regulations concerning the licensure and use of vaccines within their territory. While it may be possible for some countries to acquire new, additional regulatory capabilities to address a pandemic, for others this may not be possible at all 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, non-clinical, clinical, and post-marketing specifications, as outlined in subsequent sections of this document, are agreed as the international expectations for regulatory evaluations of candidate influenza vaccines. Non-clinical and clinical studies conducted in accordance with the requirements of this document should be considered acceptable for the purpose of evaluating candidate vaccines. National regulatory authorities are encouraged to limit requests for additional data to those which are clearly justified to address safety or efficacy concerns unique to that jurisdiction.

- Pre-qualification of pandemic and seasonal vaccine manufacturers for non-influenza vaccine producing countries

To assist developing countries in pandemic vaccine preparedness, WHO will establish a process to pre-qualify human pandemic influenza vaccine manufacturers and the regulatory authority of that country during the pre-pandemic phase. While there is no guarantee that any manufacturer will be able to supply vaccine to a non-domestic market, pre-qualification will enhance the level of regulatory confidence in a vaccine should this situation arise and ultimately enhance availability. The pre-qualification process will include pandemic influenza vaccine specific-modifications but be based on the existing WHO process for seasonal influenza vaccines, as outlined in the "Final

draft: special considerations for expedited procedure for evaluating seasonal influenza vaccines".[1]

In addition to aiding developing countries to prepare for a pandemic, the pre-qualification process will aid NRAs, in the event of a supply shortage, in acquiring alternate, non-domestic vaccine supplies. Pre-qualification may be helpful in identifying sources of vaccines that may be available for developing countries in particular and ensure that only vaccines of assured quality are used. Pre-qualification would also provide a level of assurance that any vaccine exported from a country, even if not manufactured for domestic use, met a basic level of acceptable quality as defined by WHO.

- Pre-qualification of vaccines for novel influenza viruses

Consideration should also be given to the pre-qualification requirements of vaccines for novel influenza viruses. While many developing countries are planning their own pandemic manufacturing, this may not include manufacturing of vaccines for novel influenza viruses. Upon the declaration of a pandemic, there will be a lag time until any vaccine is available, and for developing countries, in particular those at the source of the pandemic, vaccines for novel influenza viruses could be the only vaccines available. With various manufacturers proceeding with development of vaccines for novel influenza viruses based on the H5N1 strain, potential uses of this vaccine in the early stages of a pandemic must be maximized. Stockpiling of vaccines for novel influenza viruses is an option for pandemic preparedness, and this approach is being pursued or considered by some countries. Pre-qualification of bulk producers and "finishers" and stockpiling of bulk material should also be considered. Pre-qualification of vaccines for novel influenza viruses by WHO could enhance the ability of countries to accept supplies of vaccines for novel influenza viruses.

- Information Sharing

It is imperative that mechanisms be in place for regulatory agencies and vaccine manufacturers to share data from clinical trials with different vaccine types (e.g. whole virus, split antigen or subunit vaccines, cell culture derived), formulations (e.g. antigen content, adjuvants) and dosing regimens 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 preparedness and licensure plans.

It should be recognized that the pre-pandemic phase of vaccine development 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 vaccine manufacturing (with no pre-pandemic step), information sharing between NRAs and developing countries is essential to maximize successful vaccine production and to the greatest extent possible, vaccine quality, safety, and effectiveness throughout the global community.

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

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. The industry may initiative. For example, in a pandemic situation the key strengths of a vaccine would be production capacity, production speed, fast availability of reagents, and low cost. The key strengths of a vaccine for a pre-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 of information sharing.

Options to facilitate global information sharing and their feasibility could possibly be identified and evaluated by a Pandemic Influenza Vaccine Information Sharing Task Force. Although extremely difficult and a large undertaking, a global Memorandum of Understanding may also be a possible mechanism for sharing information. 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, access to vaccines, and other benefits.

- Standard Process

Building on the aforementioned factors necessary for harmonization of regulatory pathways, the skeleton of a standard process for pandemic influenza 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, and importantly highlight steps where the sharing of information globally is critical.

B.4 Criteria for emergency use

The global regulatory community agrees that as much data as possible should be obtained prior to a pandemic with the goal of licensing candidate pandemic vaccines. However, it is recognized that, since the likelihood and timing of a pandemic or how quickly it may spread cannot be predicted, a high probability exists that all needed data may not be available and that the full licensure process requirements will not be able to be met before vaccine is needed. In such instances, some sort of emergency use evaluation and authorization process may be required.

While it may seem desirable that internationally accepted criteria for an emergency use release be established, this is difficult for a number of reasons. Firstly, within each jurisdiction, existing laws and regulations will dictate what, if any, emergency options are available. While some NRAs may have a range of regulatory options which could be used in an emergency (see section C.6.3.6), other countries may be restricted in this area. It is recommended that countries carefully review their available options and, as a matter of urgency, implement any corrective measures that may be needed as soon as possible. Secondly, once it is determined that an emergency option needs to be invoked, which options to be used will depend on availability of data on the vaccine, if any, and to what extent the vaccine needs to be distributed under such option. A developing country at the source of the pandemic may need to commence a large scale

immunization campaign. Other countries may use the emergency option only for certain groups of people needed to be immunized on a priority basis. Therefore, rather than establishing data criteria for the use of an emergency option, it is the data available which will dictate which emergency use option is most suitable.

A proposed standard process to guide jurisdictions in the use of an emergency option is provided as Appendix III to this document.

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

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 pandemic influenza vaccines and vaccines for novel influenza viruses.

- Supported by laboratories of the WHO's GISN, companies that intend to produce vaccines for novel human influenza viruses or pandemic influenza vaccines are expected to use reference vaccine strains that match circulating pre-pandemic or pandemic influenza variant viruses.

- The production and handling of live influenza viruses during the initial manufacturing stages of inactivated vaccines for novel influenza viruses require an appropriate containment facility (Biosafety level (BSL) 2+ for modified prototype strains; BSL3 for wild viruses) as defined in WHO biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines (8). Independent evidence that manufacturer of vaccines for novel influenza viruses is in compliance with the appropriate biosafety standard is also required.

- Quality specifications and non-clinical considerations applicable to production and control of inactivated vaccines for novel influenza viruses and pandemic influenza vaccines using embryonated chicken eggs or cell culture substrates are included in existing documents. Current WHO recommendations for the production and control of inactivated influenza vaccines (*3*) which include specifications for pandemic human influenza vaccine production and control should be met. However, if indicated on the basis of a risk-benefit analysis of a clinical development program, some of these specifications may need to be modified. For example, the specification for total protein content in the above document allows up to 100 ug of total protein per virus strain per human dose. If local and systemic adverse events were unusually high and/or severe adverse events unknown with other influenza vaccines occurred in a clinical trial of a vaccine for a novel influenza virus, the

vaccine virus may need further purification and more stringent specifications should be applied.

- 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 pandemic influenza vaccines and vaccines for novel influenza viruses. Specific WHO information requirements on a standardized label for stockpiled vaccine or surplus vaccines released to international markets are not currently available. National regulatory authorities would require that any manufacturer producing vaccines under contract to them would label in accordance with the particular requirements of their jurisdiction.

C.1.2 General considerations for novel production systems

- If primary cell substrates are being explored for influenza vaccine manufacturing, the relevant WHO specifications would apply. It should be noted that production of influenza vaccines in primary cell substrates is a novel technology and the safety and efficacy of such vaccine candidates has not been fully evaluated. Therefore, it shall be understood that the provision of this advice should not be interpreted as any sort of endorsement of, or recommendation for, the use or development of influenza vaccines produced in primary cell cultures.

- To become more independent from the embryonated chicken egg substrate, production of vaccines for novel 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 be applicable. 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 haemagglutinin (rHA) protein; removal of residual nucleic acid, host cell protein, detergents, and other trace residuals
    - Quality control procedures: determine glycosylation patterns, purity, amino acid analysis, and molecular size of recombinant proteins

- Specifications for the purity of the rHA which may be expected to be ≥ 95%
- Adaptation of such 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 human pandemic influenza

Independent from virus growth substrate and vaccine production method, storage periods assigned to vaccine intermediates and products should be justified by real time real condition data as well as stability data under elevated temperatures. Pandemic influenza vaccines 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 non-clinical and/or clinical reinvestigation of a stockpiled vaccine might be necessary. The final stability testing program should be agreed on by the NRA.

C.2 Preclinical and nonclinical evaluation of human pandemic influenza vaccines

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 the vaccine clinical testing in humans. 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 non-clinical evaluation of vaccines as well as the international regulatory expectations in this area as provided in the WHO Guidelines on non-clinical evaluation of vaccines (*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*).

C.3 Preclinical and nonclinical considerations for vaccines for novel influenza viruses

The data in a regulatory dossier of a vaccine for a novel human influenza virus shall all be derived from a vaccine prepared with a virus variant antigenically and genetically closely related to the influenza virus against which protection is claimed. Any data with other strains that may or may not belong to the same antigenic and genetic group or another subtype could be considered supportive.

It is expected that non-clinical 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 of the 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 human pandemic influenza vaccine candidate should be discussed.

In line with WHO policy on multidose presentations, an effective antimicrobial preservative may be needed based on a risk assessment of possible microbial contamination during use and maximum recommended period after first use of the vial (in-use shelf life). For evaluation of new additives (i.e. excipients and antimicrobial preservatives), the WHO guidelines on clinical evaluation of vaccines: regulatory expectations (*15*) should be followed.

Immunogenicity data derived from an accepted animal model that responds well to human influenza vaccine (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 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 a vaccine for novel influenza viruses 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 and the assays need to be appropriately validated and standardized in such a way that enables comparison of data between different studies.

For vaccines for novel influenza viruses, protective efficacy 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 evidence for potential vaccine efficacy in humans should normally be conducted using both the original wild strain from which the vaccine virus was derived and a more antigenically distant wild type variant to the vaccine strain.

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 non-clinical endpoints selected for the animal studies, e.g. death, weight loss, virus excretion rates, clinical signs such as fever, oculo-nasal secretions, and others to estimate non-clinical efficacy shall 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 vaccine (apart from the strain), non-clinical safety investigations need not be repeated, provided that they have been performed in accordance with relevant WHO (*15*) and national/regional requirements.

Changes related to the dosage of whole virion, split or subunit human pandemic influenza vaccines derived from a licensed process may not require repeating the non-clinical safety testing provided that the total HA content per dose does not exceed an amount agreed by the national control authority. The HA content threshold may be based on evidence from seasonal influenza vaccines and for this HA content (plus

corresponding impurities) safety has been confirmed over many years with many different influenza drift variants. If a candidate vaccine exceeds this threshold, a study on local tolerance of single and repeated dose administration may be required. Investigation of local tolerance of repeated doses administration may also be required when the intended vaccination schedule consists of multiple doses of vaccine containing with total amount of HA antigen higher than the agreed on by the national control authority. This threshold is based on the evidence from seasonal influenza vaccines. In view of the possible use of vaccines for novel influenza viruses in pregnant women, animal reproductive toxicity studies should be performed.

Evaluation of a pandemic human influenza virus vaccine 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.

Inactivated influenza vaccines –including vaccines for 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 because extensive downstream purification steps are used. 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.4. Clinical evaluation of human pandemic influenza vaccines

C.4.1 Clinical development programs for pandemic influenza vaccines

The general principles to follow in the evaluation of clinical trials, both during the clinical development of a new vaccine and during the regulatory review of dossiers submitted in support of applications fort marketing authorizations are provided in the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (*16*). 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 for novel influenza viruses.

Some early studies of influenza infection, including human challenge studies following seasonal inactivated influenza vaccination suggest that HI antibody titers of 1:15 to 1:65 may be associated with protection from illness in 50% of subjects and that such protection increased with higher HI titers. Consequently, seroconversion rates and geometric mean titres (GMT) are used as measures of vaccine protection activity for seasonal influenza vaccines. It is also evident that the amount of vaccine antigen per dose has a strong impact on the immune response. Dose-response relationships may differ in younger and elderly individuals and thus should be explored in an age specific-manner.

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 risk of using them, especially during a

pandemic. However, there is a theoretical concern over the quality of the immune response generated by some adjuvanted influenza vaccines.

It has been argued that whole-virus 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 based on the extrapolation from non-human primate studies with other whole-virus adjuvanted vaccines (RSV, Measles, SARS). In these cases, internal proteins e.g. nuclear proteins, are most likely responsible for the 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.

C.4.2 Special considerations for novel technologies

Human pandemic influenza vaccines derived from more advanced technologies might not be evaluated clinically in the same way as traditional inactivated vaccines (via HA and HI assays). Ideally, the efficacy of a new technology-derived vaccine would be established initially against seasonal influenza in the pre-pandemic phase. Pre-clinical efficacy data of such pandemic 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 level 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. Titers 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 this type of pandemic candidate vaccine 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 anti-virals because these drugs would most likely abolish vaccine efficacy.

C.4.3 Pediatric studies

This section of the document defines considerations for pediatric clinical development of human pandemic influenza vaccines. The focus is obtaining licensure in the respective regions; however, it is recognized that there are other regulatory mechanisms that may allow widespread use in an emergency. It is also recognized that there are differences among regulatory authorities for studies in pediatric populations.

It is important to acknowledge that very young infants are "naïve" for every seasonal strain on a yearly basis. In addition, infants contribute substantially to the disease burden of seasonal respiratory disease and mortality together with elderly subjects. In the case of a pandemic strain, children might even be at a relatively higher risk than the elderly.

This section of the document proposes the evaluation of a strain-specific serological immune response in children against the criteria described for the clinical development programs. It is recognized that interpreting immune responses, especially for pandemic influenza strains, has limitations and that the validity of these criteria for clinical protection has not been established. Nevertheless and based on current knowledge, they are considered most suitable for the assessment of human pandemic influenza vaccines.

Pediatric data is needed for the following reasons:

- their immunological response 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; and,
- as in adults, the relevance of immune response criteria to evaluate pandemic influenza vaccines is uncertain.

For the purposes of this document, individuals under 18 years of age are considered children. Further, 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)

C.4.3.1 General considerations for pediatric pandemic vaccines

In most regions of the world, the clinical development program of a vaccine generally takes place in a stepwise fashion from adults to children. Over the past decade, this development pathway has led to the 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 the initiation of pediatric clinical studies of a human pandemic influenza vaccine.

Data from adults will provide the basis for selecting an appropriate starting dose and schedule for pediatric populations. Safety data in adults should be obtained from carefully monitored studies with pre-specified safety assessments. The stage of clinical development and the size of the safety database in adults to support vaccine use in the children warrant discussion with the relevant regulatory authorities. The evidence needed for a particular manufacturer's vaccine to support trials in the pediatric population should depend on the availability of clinical data in adults for that specific pandemic influenza vaccine and for seasonal influenza vaccine formulations of the manufacturer.

C.4.3.2 Ethical considerations of conducting pediatric studies

Ethical considerations on the conduct of vaccine evaluations as described on the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (*15*) 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 human pandemic influenza vaccine in children, the following considerations[2] 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 assessing protection in children need to be described.

The scientific conduct of studies in pediatric populations will need to address issues of human subject protection, including special protections of pediatric populations, in compliance with relevant national or regional regulations. The framework for Institutional Review Boards, or equivalent ethical oversight groups, would be followed when making decisions about clinical investigations in children. Ethics committees should take considerable care when reviewing a pediatric protocol. Appropriate provisions should be made for soliciting permission from parents or guardians and for obtaining assent from children participating in clinical studies. At each different step, the following ethical issues must be considered (See the ICH E11 guidelines for additional guidance (*18*).

- The trial should be explained to the child as far as possible and assent obtained when possible.
- Risk should be minimised by using trained staff, appropriate study design and rapid termination if necessary.

[2] Described in the EU/2001/20 directive: www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf

- Distress should be minimised by appropriate measures.
- No incentives, financial or otherwise, should be given. Reasonable expenses, on the other hand, such as reimbursement of travelling expenses are allowable.

C.4.3.3. Special considerations for pediatric participation in clinical studies of vaccines for novel human influenza viruses

Studies to evaluate immunogenicity and safety in children and adolescents should be initiated only after acceptable data have been obtained from studies conducted in healthy adults. Studies in infants and toddlers should only be initiated when data from older children and adolescents have been 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 extrapolation that is allowed will have to be considered on a case-by-case basis and will depend on the 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 for novel influenza virus that contains the strain intended for the final product. Data generated during clinical studies conducted with vaccines that contain other influenza strains may be considered supportive.

The public health benefit of children participating in clinical trials with vaccines for novel human influenza viruses as 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 true pandemic strain may differ from one with very limited for person-to-person transmission capability.

C.4.3.4. Timing of pediatric studies

It is anticipated that, as for seasonal influenza vaccine, data for human pandemic influenza vaccines will be collected first in adults and then in pediatric populations in a step-wise fashion. The amount of data to support licensure of a particular manufacturer's candidate pandemic influenza vaccine for use in pediatric populations would depend, in part, on the availability of pediatric clinical data for that manufacturers' seasonal influenza vaccine.

The ethical principles described below should be carefully considered in making decisions regarding pediatric trials. These considerations may need to be viewed from the perspective of timing of the pandemic and would change as the likelihood of the pandemic emerging increases. The need, timing and extensiveness of pediatric trials thus depend upon the information necessary at specific time points, the available evidence and the need for additional data. The amount of information obtained also depends on the predicted time until a pandemic starts. 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[3] including:

- Whether the indication being sought is identical for all age bands and whether adult efficacy data can be extrapolated to children.
- The type of trials/information needed for a relevant clinical outcome, e.g. efficacy or immunogenicity, comparability of side effects, long term safety.
- The nature of disease whether is serious and/or life-threatening; whether there is an urgent need for treatment and/or prophylaxis.
- The clinical findings in adults populations, e.g. major safety problem identified in adults.
- The availability and/or necessity of a pediatric formulation.

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

There may be national or regional differences with regard to the anticipated timing of pediatric studies with vaccines for novel influenza viruses. In one country, for example, the law outlines that all sponsors have obligations to study pediatric populations.[4] Some countries with influenza (human and animal) outbreaks have indicated a special interest in conducting pediatric studies with vaccines for novel influenza viruses. For example, studies with vaccines for novel 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. Thus, in this situation, bridging adult and/or foreign pediatric data may be critical for regulatory decision making.

In general, clinical data from seasonal influenza vaccines in children could be useful for planning pandemic influenza vaccine studies. Such data may 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 characterisation: it is of major importance that standardized methods to assess the critical immune responses e.g. serological assays are in place prior to the initiation of the pediatric studies.

[3] 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

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

- Safety: a system of recording and analysing information on adverse events post-vaccination is also of primary importance (*21*).

An improved understanding of seasonal 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.

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 obtained from studies in adults inoculated with different possible pandemic vaccine strains, more than one vaccine 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 for novel 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 constraints, data from pediatric clinical trials using vaccines for 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). It is recommended to seek advice from the competent authorities. 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 for a novel human influenza virus in young adults, a single dose pediatric clinical trial might be envisaged.

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 for 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 use in pediatric populations would be 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 for novel influenza viruses in healthy adults. These data should be used to determine the optimal serological assays and methodologies for use in pediatric studies.

C.4.3.5 Pediatric studies during the influenza pandemic

The general protocols and plans for clinical studies in children should be in place as part of a Risk Management Plan prior to the influenza pandemic (see also section C.6.3.6.). Preparation of such plans requires collaboration between all stakeholders (i.e. WHO, Public Health Authorities, NRA's and Industry)

The following specific considerations should be taken into account:

- Feasibility: an estimate of whether pediatric studies would be feasible during a pandemic.

- Choice of schedule: One important issue is whether studies in children should address immunogenicity of the predefined schedule used for adults or define the optimal schedule for children for each vaccine. The latter is traditionally done in vaccine development. Age stratified analyses should provide more insight into the importance of pre-existing immunity (whatever age) and non-maturity of the immune system in the very young in relation to the chosen schedule. However, it should 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.

- 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 interpandemic situation or may differ from adults. Case definitions to be used in such evaluations should be defined prospectively, if possible.

C.5 Special considerations for vaccines for novel influenza viruses

Several countries are currently exploring pandemic preparedness options that include the preparation and potential use of vaccines for novel influenza viruses before the pandemic is declared. The public health benefit could be significant but relies on a number of difficult to predict parameters such as the match of influenza virus subtype present in the vaccine and the actual pandemic strain, or the affected age group. In the ideal case, a vaccinated population will benefit from a primed immune system by either being completely protected from pandemic influenza virus infections, or

experiencing less severe disease outcomes after exposure to the pandemic virus. This may be accomplished by rapidly responding to booster vaccination or exposure to pandemic influenza virus. Potential risks linked to the use of vaccines for novel influenza viruses in the pre-pandemic period are adverse reactions induced by a vaccine that provides no immediate benefit or no benefit at all in case the vaccine virus strain does not match the actual pandemic virus strain, or the vaccine has no cross protective potential against drift variants of the original vaccine strain.

Given the need for regulatory preparedness for all possible intended uses of influenza vaccines as part of pandemic preparedness, regulatory considerations for the following scenarios will be outlined:

- Use of vaccines for novel human influenza viruses in pre-pandemic phases in selected parts of a population or whole populations.
- Prime/boost concepts with at least the priming dose(s) of vaccines for novel influenza viruses given in the pre-pandemic phase and followed by re-vaccination(s) during the pandemic. This means that the effect of booster dose(s) must be shown in clinical trials to demonstrate that "priming" was effective.

In principle, the clinical development of candidate vaccines for vaccines for novel human influenza viruses should be in accordance with the WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (*15*) and relevant national or regional recommendations regarding vaccine clinical development. In the pre-submission phase, the applicants are encouraged to present and discuss with the NRAs the clinical development plan and any interim results.

The indications for use of a vaccine for novel influenza virus initially approved should strictly reflect the characteristics (e.g. age range and/or immuno-competence) of the population(s) in which available data are considered sufficiently supportive of the indication. As with all vaccines, variations to these indications that extend the population in which dose recommendations were established may be approved if suitable data are provided.

In one region of the world, serological criteria for assessment of seasonal influenza vaccines include (a) seroconversion or significant increase in antihaemagglutinin antibody titre >40%, (b) increase in geometric mean titre (GMT) >2.5 and (c) proportion of subjects achieving HI titre $\geq$40 or SRH titre >25 mm^2 should be 70%. These parameters are evaluated yearly in human clinical trials due to the annual update of seasonal influenza vaccine strain composition (CPMP/BWP/214/96; http://www.emea.europa.eu/pdfs/human/bwp/021496en.pdf). 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 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 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