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 for novel 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 ratio between 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 for novel influenza viruses should induce high GMTs and seroconversion rates, most preferably after only two doses. Moreover, it could be argued that ideally the three serological criteria for assessment of seasonal influenza vaccines as defined in guideline CPMP/BWP/214/96 should be exceeded in the target population, with GMT in addition to seroconversion rates being the most important. Based on current understanding, the public health benefit of a vaccine fulfilling or exceeding these serological criteria cannot be fully estimated. It is not known whether these are the optimal criteria or whether and if so exactly what lesser levels of antibody would produce significantly less benefits. Although unlikely, based on animal data and on results of studies of annual influenza vaccine, it cannot be excluded either that there will be limited or no public health benefit if some or all of these serological criteria are not fulfilled. Although the ferret model may not always be predictive of human vaccine responses, recent studies suggest that substantial vaccine-induced protection may be achieved against some H5N1 potential pandemic 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 trials 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 for novel 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.

Immune responses should be determined at intervals after completion of the primary series in at least a statistically valid subset of the vaccinated population to investigate the need for revaccination. 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.

As part of post-approval commitments, the applicant should characterize the immunological response. This investigation might include antigenic cross-reactivity

elicited of each vaccine for novel influenza viruses with circulating influenza viruses with human 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 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 such as type and amount of antigens, content and type of adjuvant.
- Population specific factors such as age, immunological naivety to the potential pandemic strain(s).
- The circumstances of use. For example, a short duration regimen would be needed to urgently achieve seroconversion in people who might come in contact with the virus e.g. poultry workers, veterinarians, animal caretakers, human health care providers.

In general, for each specified population group naïve individuals (i.e. HI titre < 1:10) should be studied for each dose and/or proposed schedule investigated to identify formulations (e.g. antigen dose and adjuvant amount, if needed) and schedules that elicit potentially adequate serological responses. The number of subjects studied per dose group should be statistically justified, but be at least 50. (Table 1). Once the applicant considers that an appropriate formulation and schedule have been identified for healthy adults aged 18-60 years, the safety and immunogenicity of the chosen vaccine candidate should be evaluated in larger numbers of similar age population. The total database for safety in this first population to be studied should be as shown in Table 1 and as discussed below. Depending on the population included in the initial dose-finding studies, sub-stratification by age may be appropriate to obtain more information in under-represented strata. These strata should preferably be predefined. The clinical development program should be agreed on by a national regulatory authority.

Extension of the population in which the vaccine may be indicated for use (e.g. by age group and/or risk factors) may be based on studies completed before or after initial licensure. The data requirements are summarized Table 1.

Table 1: Size of the safety database required to detect Adverse Drug Reactions (ADR) at stated frequency[5]

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

Age group	ADR frequency and sample size
Adults from 16 to 60 years	≤ one in one thousand persons vaccinated (i.e. rare ADRs) (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 ADRs) (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 ADRs) (e.g. a database of approximately 300 subjects from each specified risk group might be sufficient)

The size of the safety database for each human pandemic influenza vaccine will be different depending on the population studied, as defined in 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[6] . These data should be submitted as part of the license application. If any new issues regarding safety arise during the clinical development programme 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 for novel human influenza virus contains thiomersal as a preservative, relevant WHO and national or regional guidance should be followed.

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 plans ready to assess efficacy after exposure to circulating influenza virus of pandemic potential (see section 4). These plans are important to provide insight as to whether prior vaccination may afford at least some protection against strains that might trigger a pandemic.

Whenever the opportunity arises, NRAs should request further information on safety, immunogenicity and efficacy to expand the vaccine database. It is especially recommended to collect additional data in populations which have been studied to a lesser extent in the pre-authorization clinical trials. In the event of a declared pandemic, attempts should be made to estimate the effectiveness of prior vaccination in persons who do and do not receive a dose of any pandemic vaccine through standardized and well controlled trials. A Risk Management Plan should be provided with safety information for each major population group that have not been studied or have only been studied to a limited degree in the pre-authorization phase.

[6] Defined in guideline CPMP/BWP/2490/00; www.emea.europa.eu/pdfs/human/bwp/249000en.pdf

As for seasonal influenza vaccines, the marketing authorization holder (MAH) 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 HA subtype of influenza virus most likely to trigger a pandemic has changed. Two scenarios could occur and have different regulatory implications as follows:

a. Replacement of the strain in the approved vaccine with a different strain of the same subtype (e.g. supplanting the original H5N1 with another H5N1 strain). In this case the MAH would have to submit all manufacturing and quality data related to the new strain. 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 vaccine prepared from the replacement strain should also be administered to a cohort that previously received the original strain vaccine in order to assess cross-priming. Applicants are advised to obtain advice from the competent authorities regarding the extent and type of clinical data that would be required.

b. Replacement of the HA/NA subtype of strain (e.g. supplanting the original H5N1 strain with an H7N7 strain). Advice from the competent authorities should be sought on the regulatory framework and data requirements for such a change.

A study in relevant animal model should be conducted to demonstrate that immune responses to the new strain in the vaccine are at least as good as were those to the initial strain in the licensed product. Applicants are advised to obtain advice from the relevant national regulatory authority regarding the extent and type of clinical data that would be required. It should be noted that different requirements would likely apply if there was an intent to change the H/N type of strain (e.g. from a H5N1 vaccine to a H7N7 vaccine). Advice from the relevant NRA should be sought on the regulatory framework and data requirements for such a change.

C.6 Quality control preparedness

C.6.1 General remarks

Quality control (QC) of human pandemic influenza vaccines will be based on the processes and policies for seasonal influenza vaccines. Seasonal influenza vaccines should be produced according to the conditions of GMP, tested for quality and safety by the vaccine manufacturer and then, 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 will be done in a high pressure environment, where there will be a much higher throughput than normal and there may be technical problems connected with the novelty of pandemic vaccines, which could interfere with efficient testing. In a pre-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 will be needed for batch release tests and it may be necessary for an NCL to perform tests in parallel with vaccine manufacturers and/or to perform only a subset of the tests (e.g. SRID and LAL tests) on seasonal influenza vaccines.

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 on order to minimise disruptions in vaccine supply. Some NCLs have already developed pandemic vaccine batch release procedures, others have not.

It is also recognised 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.

C.6.2 Quality control testing by vaccine manufacturers

C.6.2.1 Inactivated vaccines

Current experience with inactivated H5N1 human vaccine development suggests that a pandemic vaccine is likely to be a virus engineered by reverse genetics and formulated as a monovalent vaccine with alum or a proprietary adjuvant. Alternatively the vaccine may be formulated without adjuvant but the adjuvant may be added in the clinic. This may affect the type of test conducted on the vaccine. The vaccine is likely to be produced in much larger quantities (i.e. more batches) than a seasonal vaccine 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 vaccines, since there is an increased risk of problems when working under extreme time pressure. However because of technical difficulties or special pandemic circumstances, some QC tests may need to be modified. In the pre-pandemic situation, there will not be the high demand for vaccine expected during a pandemic, but 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 vaccines:

- Vaccine reference virus

A fully characterized reference virus will be provided by a WHO laboratory. This is important to ensure that vaccines produced from potentially pathogenic viruses by reverse genetics are safe and have been produced according to accepted quality standards.

- Identity of seed virus

For seasonal 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 do these tests at an NCL or a WHO laboratory using primers available from virus surveillance activities or pandemic vaccine development.

- Adventitious agent testing of cell culture-derived vaccines

In a pandemic emergency, there will not be enough time to perform the in vivo tests for adventitious agents normally required for cell-derived vaccines. Manufacturers should perform a risk analysis for use of alternative tests based on the type of cells used (susceptibility to the agents) and the type of vaccine process (capacity to eliminate the agents). In one part of the world, PCR tests are allowed provided a comparison of in vivo and PCR tests is done to validate 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, ELISA assays are recommended. These surrogate potency tests should be validated by vaccine manufacturers and the relevant NCLs prior to the pandemic. When SRID reagents are available, they should be used to test bulk vaccine (also named monovalent pooled harvest (MPH)[7] in one region of the world). If in a pandemic situation, an NCL does not test final product, blending of vaccine into final formulation should be based on a potency agreed between the manufacturer and the NCL.

SRID potency tests should 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 C6.3.8, tests of adjuvanted vaccine) are 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

[7] Monovalent pooled harvest (MPH) 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.

NCLs for possible interference by the adjuvant. If interference is likely, the LAL test should be done on the bulk vaccine before the addition of adjuvant.

C.6.2.2 Live attenuated influenza vaccines

In the event that a live attenuated virus product is used as a pandemic vaccine, there will be similar issues concerning rapid production and testing of vaccine to those described previously for inactivated vaccine. 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 Haemagglutinin and Neuraminidase 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.

- 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.

C.6.3 National Control Laboratory batch release procedures

C.6.3.1 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 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 and/or testing could be done co-jointly between the vaccine manufacturer and NCL.

C.6.3.2 Batch release procedures for inactivated influenza vaccines

As described before, there are technical and logistic issues for human pandemic influenza vaccines which could affect the NCL batch release process. Although there are significant differences between batch release procedures around the world, the following is a 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 pre-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.

- First priority: Protocol review

A protocol summarising 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.

- Second priority, if time and resources allow, will be protocol review plus the following tests:

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 done on adjuvanted final product.

The NCL should perform SRID tests when reagents are available and should perform an agreed surrogate potency tests when SRID reagents are not available (see earlier sections). 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 C.6.3.8. tests of adjuvanted vaccine). 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 national regulations require the LAL test for batch release, it 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 addition of adjuvant.

iii. Trend analysis

When there is 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).

C.6.3.3 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.

C.6.3.4 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 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 NCL's 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.

C.6.3.5 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.

C.6.3.6 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. Topics that should be assessed are:

i. Are there sufficient personnel trained in influenza vaccine batch release to cope with the increased amount of testing? Backup staff should be trained if necessary. Should staff be required to work in shifts?
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. Are there adequate storage facilities at the NCLs to handle the anticipated surge in samples for testing?

C.6.3.7 Provision of reagents for SRID tests

SRID reagents for batch release of seasonal influenza vaccines are normally supplied by one of four laboratories: Center for Biologics Evaluation and Research, USA; National Institute for Biological Standards and Control, UK; National Institute of Infectious Diseases, Japan; Therapeutic Goods Administration, Australia. The reagents are developed and calibrated jointly by collaborative study among the four laboratories and normally it takes about three months for this process. 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 and 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 for calibration either performed alone or using locally-developed networks which may include vaccine manufacturers and/or other NCLs on characteristics of new pandemic vaccine viruses.

- 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 will be under enormous pressure to meet their orders in time so 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 WHO Collaborative Centres develop a new candidate H5N1 vaccine virus, there is a need for matched SRID reagents. An SRID antigen must be antigenically homologous to the vaccine antigen and therefore can only be produced when the identity of the candidate pandemic vaccine virus is known. However, this is not the case with SRID antiserum which requires a long time (approximately 3 months) for preparation. There is evidence that sheep antisera are cross-reactive between antigenic drift variants, so that antiserum prepared against one H5N1 virus may be usable in SRID tests of another H5N1 virus. WHO should play a coordinating role between vaccine manufacturers and the four laboratories normally involved with reagent production to ensure reagents are available for each candidate H5N1 vaccine strain. SRID reagents are also being developed for other virus strains recognised 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.

- Risk assessment

Each Collaborating Centre should perform a risk assessment to ensure the all foreseeable risks to 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
v Information exchange to other collaborating centres and vaccine manufacturers

C.6.3.8 Tests of adjuvanted vaccines

It is known that alum interferes with the SRID potency test and may interfere with the LAL endotoxin test, although in one region of the world, alum used in the formulation of vaccines for novel influenza viruses from two manufacturers has not posed any interference with the LAL test. During development of pandemic 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 potency tests (e.g. protein and/or SDS PAGE, ELISA assays) are developed by vaccine manufacturers, information should be shared with the relevant NCL in preparation for batch release testing.

Part D. Post- Marketing Surveillance

D.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 for novel influenza viruses studied before the pandemic.

Clinical trials with vaccines for novel influenza viruses during the pre-pandemic phase will mainly detect common adverse events following immunization (AEFI), and will probably not address either 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 human pandemic influenza vaccines. In consequence, the risks and benefits of human pandemic influenza vaccines will need to be studied post-marketing.

Because of the likely extreme conditions of a pandemic, clear postmarketing surveillance objectives to evaluate effectiveness and safety of a human 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, analysed 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). Careful consideration of important aspects of study protocols need to be agreed upon in the pre-pandemic phase. Functionality of protocols and systems should be tested in the inter-pandemic period. Sponsors should seek approval by ethics committees/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. Furthermore, it is important to determine feasible and realistic conditions of post-marketing surveillance in different scenarios.

Setting up a postmarketing surveillance plan to respond to an influenza pandemic would facilitate adequate response to public concerns and maintain the public confidence in the vaccination programme. Such postmarketing preparedness requires collaboration between all stakeholders, WHO, Public Health Authorities, NRAs. and industry.

D.2. 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 prioritisation of activities (i.e. pharmacovigilance and effectiveness) with simplification and harmonisation measure 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. Systems may also meet the postmarketing surveillance needs of pandemic influenza vaccines. It is strongly recommended that methods, tools and systems to investigate safety and effectiveness of pandemic vaccines be implemented in the pre-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 postmarketing 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 which include:

- Availability of pandemic influenza vaccines
- Different strategies of countries concerning use of vaccines for novel influenza viruses in the pre-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 immunisation 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 organisation
- Availability of data sources and surveillance in place for seasonal influenza illness and 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.

In consequence, 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, 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
- postmarketing surveillance protocols and detailed work plans indicating study feasibility starting as soon as vaccination begins should be agreed beforehand
- use of common terminology for consistent communication across regulatory bodies worldwide
- data collection that allow for

    - estimation of incidence
    - comparison and differentiation between vaccines, events associated to influenza vaccine and those associated to other vaccines
    - aassessment 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
    - comparisons 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 review 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.

D.3. Special considerations if vaccines for novel influenza viruses are used before the pandemic is declared

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 for novel influenza viruses and immunized certain risk populations (i.e. poultry culling crews, veterinarians and influenza laboratory workers) 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 for novel human influenza viruses in the pre-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, in pregnant women and in representative numbers of patients with co-morbidities is highly unlikely even unfeasible.

When feasible, the following parameters may be considered:

Immunogenicity:

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

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

The frequency of testing might be higher at the start of using vaccines for novel influenza viruses on 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 developed. It is important to identify the latest time point for boosting (e.g.

with the homologous strain vaccine) as well as the boosting effect of a vaccine with a heterologous strain, if available.

Efficacy

The effectiveness of vaccines for novel influenza viruses administered in the pre-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) in the pre-pandemic phase should be developed beforehand. This strategy will depend on how the vaccine is used in countries and may vary among countries. In general principle, it should be based on the best available information and requires collaboration of all stakeholders (i.e. competent authorities, health authorities, vaccine manufacturers, health care professionals). At 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 pre-pandemic priming in the pandemic phase.

Safety

In principle, all options to demonstrate vaccine safety should be explored and implemented in the pre-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 (AESI) are also considered important to be specifically monitored by documenting cases reported by health care professionals. Case definitions from the Brighton Collaboration should be used if available (*29*). Background data for these AESI are important for the interpretation of reporting rates.

In the case of priming large population fractions with vaccines for novel 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 AEFI. 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.

D.4. Pharmacovigilance Activities

The safety data available for human 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 ADRs, 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, periodic safety reports (PSRs), and data management), and
ii) additional pharmacovigilance studies (monitoring system for severe AEFIs, epidemiological studies with feasibility analysis)

D.4.1. Routine Pharmacovigilance

D.4.1.1. Spontaneous reporting

The potential postal service disruption and limited availability of health care professionals in a pandemic require the development 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 other 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 pre-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 AEFI (e.g. febrile convulsions, Bells palsy, and Guillain-Barre 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 ADRs 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 http://www.who-umc.org/DynPage.aspx). In absence of a national pharmacovigilance centre, EPI programmes are also encouraged to submit AEFI 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 CIOMS format http://www.cioms.ch/cioms.pdf) might be acceptable where no ADR database is accessible.

A list of specific potential adverse reactions of particular interest should be drawn-up for 'active' reporting e.g. convulsions, anaphylaxis, neuritis, Bell's palsy, Guillain-Barré Syndrome, 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 (SMQs). 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 companies 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.

D.4.1.2. Periodic Safety Reports

Periodic safety reports (PSR) by manufacturers may provide an opportunity for aggregated summary safety data. These reports should be vaccine brand-specific, simple to prepare and simple to assess. The periodic safety reports should be more than a duplication of AEFI 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 weeks (e.g. 4 -6 weeks) after start of vaccination and less frequent thereafter. The report may contain the number of all AEFIs in the period covered by the PSR, 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 Excel spreadsheet may present tables of ADRs with a unique case identifier and a limited number of fields. Vaccine distribution data by batch and country (period covered by the PSR and

cumulatively since launch) should be provided. Companies 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' Periodic Safety Update Report 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 NRAs to compare between vaccines for possible differences in safety profiles.

D.4.1.3. 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 AE 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 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 AEs. 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 computerised methods of signal detection should be tested in the pre-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.

D.4.1.4. 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.

D.4.2. 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 (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 viral vaccines, adjuvanted vaccines).

D.4.2.1. 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
- 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 the 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
- development of study databases in the interpandemic 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.

D.4.2.2. 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 interpandemic vaccines or
- whether it is comparable with the clinical phase I-III data of a vaccine for a novel 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
- Observed versus expected analyses

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

D.4.2.3. Target population

The target population for a post-marketing study should include groups not covered in clinical trials conducted in the pre-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 reactions (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.

D.4.2.4. Randomised clinical trial

As randomized clinical trials (RCT) 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 available yet. 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 randomise them also. Effectiveness and immunogenicity of pandemic-specific strains may also be addressed in RTC. The study protocol should be agreed upon in the pre-pandemic phase.

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

D.4.2.5 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 pandemic vaccines in a pandemic. It might be possible to