identify a cohort who will receive vaccination very early (e.g. high risk group, first responders) and an unvaccinated cohort who will receive vaccination later.

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

D.4.2.6. Prospective (observational) cohort study design without control group

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

D.4.2.7. Case-control study design

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

D.4.2.8 Use of large computerised database

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

D.5. Immunogenicity and efficacy/effectiveness

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

In addition to existing surveillance systems to monitor the onset and evolution of the pandemic, PHA should instate enhanced surveillance tools to analyze the 'effectiveness' of vaccination campaigns. Protocols should be developed in the pre-pandemic phase. The study design may need to be reviewed in light of the anticipated

epidemiological features of the pandemic (e.g. virulence and transmissibility characteristics that require re-review of clinical trial organization and sample size). Methods to use will depend on existing vaccination strategy and tools. For example, if the entire population was vaccinated, non-vaccinated groups would not be available for comparison cohort studies (although pre-vaccination person-time could be useful). The analysis of data from electronic registries or highly linked databases may only be feasible in a few countries. Different methods and strategies may be used in different countries.

D.5.1. Study design

Vaccine effectiveness may be estimated from observational cohort studies that describe disease occurrence to be prevented in the target population over time. Alternatively, vaccine effectiveness may be estimated during a phased introduction of the vaccine into the target population in which the non-eligible groups (first wave) might form the strata for randomisation. Without a randomization step, considerable biases may be introduced. In addition, a prospective cohort design with pre-defined allocation for vaccination might also be conducted, especially in the situation of prioritization of the target population for vaccination. If plans for prioritization of vaccination in the first wave (e.g. first responders will receive vaccination early) exist, identification of the cohorts and detailed planning of the study should be possible in the pre-pandemic phase.

Continuous assessment of vaccine effectiveness during the whole pandemic is essential to detect possible virus drift and to enable PHA to modify, if necessary, the vaccination program. The extension of the follow-up period into a subset of the cohort population may address this objective. Possible virus drift can also be investigated by identification and follow-up of cohorts of subjects successively immunised with the pandemic vaccines. This objective may also be addressed via sentinel reporting of clinical disease during the whole pandemic. Clinical data should be linked with laboratory surveillance data.

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

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

In order to make appropriate decisions real-time data should ideally be collected, evaluated and analysed by NRA's and/or Public Health Authorities. Any delay may cause a serious delay of the decision making process and may have serious public health implications.

D.5.2. Endpoints

Laboratory confirmation of influenza may not be feasible as the primary endpoint for post-marketing effectiveness surveillance, but only for a subset population to be defined. Laboratory surveillance may provide important information concerning possible drift variance of the virus and subsequent loss of effectiveness of available vaccines.

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

D.5.3. Conduct of studies

Analysis of all cases should be provided regardless of time in relation to vaccine doses. All vaccine failures (as defined) and any other breakthrough cases should be investigated in detail.

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

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

D.5.4. Vaccines with a composition similar to the pandemic strain

Vaccines with a close but not perfect strain match with the pandemic strain may be used in some countries on grounds that at least some degree of protection might be afforded. In such situations, investigations on the effectiveness of priming with these vaccines versus non-priming should be conducted.

D.6. Consideration of post-marketing surveillance in different target groups

In a pandemic situation, it is very likely that health authorities may have to make recommendations on the use of the vaccine in population groups not previously studied in clinical trials. Post-marketing surveillance of safety and effectiveness in particular

target groups is recommended to enable competent regulatory authorities and health authorities to review the adequacy of public health decisions.

D.6.1. Age

Immunological responses to vaccines depend on the independent and coordinated function of innate and adaptive immune response which is different in infants and adults. Differences of the immune response in different age categories might translate into differences of efficacy and safety of certain types of pandemic influenza vaccines. Targeted surveillance of effectiveness and safety in different age categories is thus warranted.

D.6.2. Pregnant women

Based on seasonal influenza morbidity pregnant women are considered to constitute a risk group for influenza related complications and public health authorities might therefore recommend vaccination in pregnant women. On the other hand, pregnant women will most likely not be included in clinical trials with human pandemic influenza vaccines. Although inactivated vaccines are considered to cause no harm when administered to pregnant women, the knowledge concerning reproductive toxicity of inactivated pandemic influenza vaccines (as they will be new vaccines perhaps in new formulations) in humans will be limited. It is unknown whether conclusions from animal studies conducted during non-clinical evaluations of pandemic influenza vaccines will apply to humans. As a consequence there will be very limited or no data available regarding safety and efficacy of pandemic vaccines in pregnancy prior to use.

Continuous evaluation of risks and benefits of pandemic influenza vaccines should be established in pregnant women. As a first step more information may be gathered with seasonal influenza vaccines. In this respect, capability of already existing pregnancy registries or currently running epidemiological studies should be evaluated. The studies with pandemic human influenza vaccines should be designed to identify spontaneous abortions, stillbirth, and congenital malformations.

D.6.3. Other target groups

Effectiveness and safety should, ideally, also be established in the patients with chronic diseases and immunocompromised as risk benefit balance might deviate from the healthy population.

D.7. Considerations for specific pandemic influenza vaccines

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

D.7.1. Live attenuated vaccines

Live attenuated vaccines may cause vaccine-associated disease of less severe, if any, in vaccine recipients compared to the natural infectious disease. However, some LAIV are very rarely linked to serious syndromes closely resembling wild-type disease probably associated with individual host factors of increased susceptibility. If a live attenuated human pandemic influenza vaccine is deployed during a time when the wild-type virus is circulating, some individuals may be vaccinated at a time when they are incubating the wild-type strain. Validated and standardised assays should be developed and implemented prior to the use of such vaccines to differentiate between vaccine virus and wild-type virus to properly assess these cases.

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

D.7.2. Immunological adjuvants

Post-marketing surveillance will depend on the type of adjuvant and the results of the non-clinical and clinical investigation of the human pandemic influenza vaccine. New adjuvants that stimulate a specific immune response will justify attention to specific issues such as auto-immune diseases that are potentially rare and adverse events that can occur a long time postimmunization. Particular attention is required if pre- and clinical investigation has indicated that the adjuvant can bias the immune response towards a Th2-response. Enhanced surveillance in certain subgroups such as infants may be necessary, in this case. Synergistic immune mediated reactions of adjuvant and the biologically active antigen have to be considered.

D.8. Risk Benefit Assessment

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

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

The benefit of a pandemic vaccine may decline for an individual as vaccine coverage rises, the disease incidence decreases and herd immunity occurs. Despite a decrease in disease incidence, the public health benefit of vaccination might remain high if the

probability of disease re-emergence increases when vaccine coverage rate in the population becomes too low. Thus the benefit risk balance of a pandemic vaccine has both public and individual health aspects.

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

D.9. Responsibilities of key stakeholders

Key stakeholders in the process of post-marketing surveillance include:

- Vaccinees
- Health professionals
- Manufacturer(s)
- NRAs
- Public health authorities
- Immunization delivery programs (such as EPI)
- Governments
- Media

Depending on responsibility, stakeholders have differing roles that contribute, through properly communicated and coordinated risk reduction strategies, to the safest and most effective use of products. It is important that all stakeholders agree beforehand on the principles of vaccine safety information exchange during a pandemic. All efforts should be made to coordinate information exchange and mutual recognition of study results to avoid duplication of work and enable evidence-based decision making.

Regulatory authorities in vaccine receiving countries may accept vaccine qualification from producing countries. In such case, manufacturers may not be requested to repeat adequate safety and efficacy studies performed in a producing country with competent regulatory oversight.

D.10. Principles of communication

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

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

Critically important is clear explanation of what is known about the pandemic vaccine safety and efficacy when it is first used and what processes are in place for gathering outstanding data without causing panic. An essential part of the latter would be giving clear instructions for reporting suspected vaccine adverse reactions.

Communication might differ in different vaccine use scenarios and vaccine products (e.g. whole virus, cell culture, adjuvanted vaccine). Thus, transparency of information and definition of stakeholders' roles and responsibilities are essential.

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

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

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

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

See Appendix IB for a tabular summary of the information presented in this section.

Australia

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

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

Timelines: For review of Category 3 submission 45 working days after receipt of the application

Annual Influenza Vaccine Licensure: In the case of a new flu vaccine, TGA require a full submission including quality data, preclinical data and clinical data. Data expectations would accord with general CPMP guidance for new vaccines. Annual strain changes require an application with quality data consistent with CPMP/BWP/ 214/96 - *Note for Guidance on Harmonisation of Requirements for Influenza Vaccines*. Because of the production time frames, if there are changes to strains from those used in the Northern hemisphere winter there may not be a clinical efficacy study submitted with the quality data.

Proposed Pandemic Regulatory Pathway: TGA accepts the EMEA guidelines on pandemic vaccine licensing. As with the EMEA, licensure of a pandemic influenza vaccine will be based on approval of a core dossier for a pre-pandemic vaccine with quality, safety and efficacy data for the pre-pandemic vaccine to be provided and authorised during interpandemic period.

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

The TGA and WHO Collaborating Centre for Reference and Research on Influenza will cooperate with the manufacturers in providing laboratory reagents for standardization of inactivated vaccine and reference strains for antigenic analysis.

Special requirements regarding quality and manufacturing data:

For pre-pandemic vaccine:

- Products containing ingredients of human or animal origin evaluated for TSE safety

Special Clinical Data Requirements:

For pre-pandemic vaccine:

- human immunogenicity and safety studies including all age groups (especially children) and patients with some disease states, (to give confidence in the registration decision)

Accelerated Approval Options/Emergency Use Provisions:

Canada

Regulatory Authority: Influenza vaccines are regulated by Health Canada/Health Products and Food Branch/Biologics and Genetic Therapies Directorate (BGTD) pursuant various provisions of the *Food and Drugs Act & Regulations (FDA & R).*

Submission Type and Application: New vaccines are ~~approved~~ authorized for marketing in Canada following the review of a New Drug Submission (NDS) by BGTD. An NDS must include a complete data set in support of the safety, efficacy and qualify of the vaccine as well as Product Specific Facility Information that outlines the method of manufacture of the vaccine in significant detail. Further, an On-Site Evaluation is completed to assess the production process and the facility as it impacts on the safety and efficacy of the product. The manufacturer must also provide samples of at least three and preferably five batches or "lots" of the vaccine for testing in the laboratories of BGTD.

Annual Influenza Vaccine Licensure: Although the regulatory requirements for new vaccines are clear, influenza vaccines have been marketed in Canada for over 50 years and their approval pre-dates some of the regulations being applied to new vaccines. Additionally the need to reproduce the vaccine each year with the new circulating strains has necessitated a special approach to the regulation of these vaccines. Changes to the vaccines to reflect the year to year strain variation were approved via the filing of an amendment to the existing license, in which manufacturers would submit for review only their revised labelling material once the strains which would be included that year were known. There was no requirement for the submission of any clinical data for vaccine with the new strains.

During the 2000-2001 flu season, an increased number of influenza vaccine associated adverse events described as oculorespiratory syndrome (ORS) were observed. These adverse events led to a re-evaluation of the requirements for the annual approval and for the years since 2000-2001 manufacturers are required to submit clinical trial data for their products, to assess the tolerance and efficacy of the vaccine in two groups of health volunteers, aged between 18 and 60 and over 60, as per the CPMP guidelines.

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

a. data to support the quality of production of the vaccine, as it relates to the new strain, plus any improvements/alterations to the production process;
b. data from two small clinical studies (generally ~ 50 patients each, in 18 - 60 yr old and > 60 yr old patient groups), to assess the tolerability and immunogenicity of the vaccine; and,
c. revised labelling material (inner and outer labels, and a revised Product Monograph or Direction leaflet).

Proposed Pandemic Regulatory Pathway: The unknown factors surrounding a pandemic vaccine, including whether changes will be needed to the manufacturing process currently used increase the likelihood that a pandemic vaccine will have many have significant differences from a seasonal influenza vaccine. Therefore the regulatory process for a pandemic vaccine, while in many respects similar to that of the seasonal influenza vaccine, will accommodate these factors and assumptions. The regulatory process for approval of a pandemic vaccine will be that of an NDS and not of an amendment to an existing license for a seasonal influenza vaccine

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

In advance of an actual pandemic, protocols must be in place to both investigate immunological responses to the pandemic vaccine to support authorization and to study the level of clinical protection during an actual pandemic, as part of post-market conditions.

Clinical Trial Applications for trials to be conducted with the actual pandemic strain should be developed and filed for review during the interpandemic phase and should be updated as needed based on developing knowledge. This will provide for protocols which can be implemented immediately upon declaration of the pandemic.

Estimation of vaccine effectiveness may need to be carried out by studying pre-determined target populations during the pandemic. These should be addressed as part of the NDS filing, as conditional post marketing studies.

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

Canada will follow.

Special Requirements regarding Quality and Manufacturing data:

- the manufacturing process review for regulatory authorization of seasonal influenza vaccine including advance On-Site Evaluation(s) of the production facilities, will be the basis of the expedited assessment of the chemistry and manufacturing for the pandemic influenza vaccine
- the relevant information relating to the seasonal influenza production lots, with the addition of specific data regarding the pre-pandemic vaccine, monovalent bulks and drug product is considered supportive and may be cross referenced.
- protocols, including a Certificate of Analysis, identifying adequate specification controls and limits, and specific batch information, are expected to be provided for the manufactured lots of:
- the pre-pandemic vaccine used in clinical trials
- the pandemic vaccine clinical trial material
- the pandemic vaccine intended for mass immunization
- both the prototype (mock) and the pandemic influenza vaccines are subject to the Lot Release requirements of the *Food and Drug Regulations*, Section C.04.015, as provided in the document *Guidance for Sponsors-Lot Release Program for Schedule D (Biologic) Drugs* (2005). In situations of pandemic emergency, targeted or sentinel testing of commercial lots will be performed. Additionally, testing may be performed on the bulk production batch(es).
- any changes to the physical entity of the drug substance, its derivation, or analytical methods for identity and characterization, and any changes to the drug substance or drug product manufacturing processes, or specification controls, for the designated pandemic influenza vaccine, shall be submitted to Health Canada for comparative review and assessment.
- product-specific facility information, for the production of the pre-pandemic and pandemic influenza virus vaccines, for clinical trial and marketed lots shall be required;
- stability data and protocol for stability testing of pandemic vaccine
- viral safety data

Special Requirements regarding Clinical Data:

- pre-clinical and clinical safety and immunogenicity data obtained with the pre-pandemic vaccine; *(if the pandemic virus strain differs from the prototype strain, an indication of the immunogenicity of the pandemic influenza vaccine will be required)*;
- The pre-clinical and clinical results derived with the pre-pandemic vaccine(s) should aid in determination of the safety of the adjuvant used in the vaccine's formulation;
    - the formulation of a vaccine appropriate for immunization of a naive population;
    - clinical trial requirements to assess the safety and efficacy of the pandemic vaccine
- a complete clinical safety and efficacy trial plan, including anticipated time lines, to generate the necessary data during the pandemic period, and to provide it for regulatory review. *(prepared during the inter-pandemic period)*
  any available clinical safety and efficacy data for the pandemic vaccine;

Accelerated Approval Options/Emergency Use Provisions:

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

Special Access Programme (SAP)

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

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

Interim Orders

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

Health Canada has a prepared a library of interim orders which could be used to allow for the licensure of a pandemic vaccine in an emergency situation (i.e. where vaccine is required before standard regulatory requirements for licensure have been met). One of these interim orders will be for authorization in an emergency situation under an "Animal Rule" type provision (see description under United States overview)

Clinical Trials

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

European Union

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

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

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

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

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

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