Annual Influenza Vaccine Licensure: Currently, all seasonal influenza vaccines in Europe as authorized via the mutual recognition procedure. A special fast track Type II variation procedure is in place for the annual strain change. The fast track procedure consists of two steps. The first part concerns the assessment of the administrative/quality data (Summary of product characteristics (SPC), patient leaflet, labelling and the chemical, pharmaceutical and biological documentation). The second part concerns the assessment of the clinical data. Results of clinical studies are required according to the *Guideline Harmonisation of Requirements for Influenza Vaccines* (CPMP/BWP/ 214/96). A similar fast-track variation procedure exists in the centralised system.

Proposed Pandemic Regulatory Pathway: The perspective of the EMEA is that a pandemic vaccine will differ significantly from an annual vaccine. The EMEA strategy relies on the evaluation of a pre-pandemic vaccine core dossier during the inter-pandemic period where quality, non-clinical testing and clinical data will be evaluated. Once the pandemic strikes, manufacturers will have to submit a type II variation to introduce information on the actual pandemic strain. The aim of the core dossier process is to provide a "fast track" authorisation of pandemic influenza vaccines as new (full) marketing authorisations, not variation to seasonal vaccine. Most scientific aspects as well as product information (doctor / patient leaflets) can be considered before a pandemic and can be approved in interpandemic period.

In 2005, EMEA published the guidance *Core Summary of Product Characteristics (SPC) for Pandemic Influenza Vaccines.* The aim of this guideline is to standardize SPCs for all inactivated pandemic influenza vaccines, thereby facilitating the submission of core dossiers. Under this guideline, product information will be approved as part of the core dossier authorization and minimal changes only needed as part of the pandemic variation approval (only information related to pandemic strain). The pre-pandemic vaccine will be produced (ideally) in same way as intended for pandemic vaccine (either cell culture or egg derived/whole virion or split or subunit vaccine) and with the same antigen content and adjuvant system (if used) as the future pandemic vaccine.
Preclinical testing to establish safety and immunogenicity and clinical trials with the pre-pandemic vaccine to verify safety and efficacy and to establish a dose and dosing schedule will be required.

Special Requirements regarding Quality and Manufacturing data:

- vaccine reference virus (development, testing)
- vaccine seed lots (production process, testing, extraneous agents)
- vaccine production: Production process
- Formulation (multidose: test for antimicrobial preservative)
- Vaccine standardisation (development of alternative tests to standardise the vaccine)
- Adjuvant
- Stability data and protocol for stability testing of pandemic vaccine

Special Requirements regarding Clinical Data:

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

- Data in children

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

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

- Accelerated review process (max 150 days, can be shortened on agreement of the CHMP; art 14(9) of Regulation (EC) No 726/20004)
- Conditional marketing authorizations (Commission Regulation (EC) No 507/2006), which allow, in case of medicinal products to be used in emergency situations in response to public health threats, for authorization on basis of a limited data package. In emergency situations, such a conditional marketing authorization may be granted even if comprehensive clinical, non-clinical and quality date are not available at the time of submission. Such marketing authorizations are linked to strict commitments to provide the missing clinical and non-clinical information within a defined timeframe.

Japan

Regulatory Authority: The Pharmaceuticals and Medical Devices Agency (PMDA) reviews pharmaceuticals and medical devices, based on the Pharmaceutical Affairs Law (PAL) (Law 145, 1960 revised 2002). The Ministry of Health, Labour and Welfare (MHLW) has the authority of approval upon the output of PMDA's review. PMDA also gives guidance and

advice concerning clinical trials. The research and development of vaccines including pandemic influenza vaccine resides with the National Institute of Infectious Diseases (NIID).

Submission Type and Application: A manufacturer will file a New Drug Application (NDA) for examination and approval of all new drugs including vaccines. The MHLW will execute a drug approval a drug for approval upon receipt of the advice from the Pharmaceutical and Food Sanitation Council in NDA review process, based on demonstrated safety and effectiveness of the product reviewed through PMDA's scientific review process.

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

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

Proposed Pandemic Regulatory Pathway: MHLW and PMDA request a manufacturer who is producing H5N1 vaccine (pre-pandemic and pandemic type) to file NDA application, pursuant to PAL. The NDA would be processed under the priority review provisions of the PAL (See Accelerated Approval/Emergency Use Provisions section). The pre-pandemic vaccine is to be manufactured in the same way as that of potential pandemic vaccine. The pandemic vaccine is regarded as the extension of pre-pandemic vaccine where regulatory process would be abridged to a larger extent on the pandemic strain, basically based on the non-clinical data provided by the pandemic strain unless otherwise defined in the process for the new strain in case of emergency.

The H5N1 Pandemic Vaccine Development in Japan is a government-driven national project under collaboration among MHLW, NIID and a manufacturers' task force of four different manufacturers. The national licensing agency PMDA gives an arrangement to give scientific advice, such as a testing protocol, to the manufacturers as a first priority. A single formulation vaccine is being developed and produced by the four manufacturers. Submission for license will be made by each manufacture.

The H5N1 Pandemic Vaccine Development in Japan is a government-driven national project under collaboration among MHLW and NIID and a manufacturer's task force of four different manufacturers. The national licensing agency PMDA supports the project as a first priority. A single formulation vaccine is being developed and produced by the four manufacturers. Submission for license will be made by each manufacture. PMDA and MHLW will be reviewing an application dossier of pre-pandemic (prototype) vaccines during interpandemic period. The pre-pandemic vaccine is to be manufactured in the same way as that of potential pandemic vaccine. The pandemic vaccine is regarded as the extension of prototype vaccine where regulatory process is abridged to a larger extent on the pandemic strain, based on the non-clinical data provided by the pandemic strain.

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

Special Requirements regarding Clinical Data:

- Immunogenicity in animal including challenge tests
- Non-clinical safety
- Clinical studies performed under cooperation and support, in part, by the Japan Medical Association
- Each manufacture's vaccine to be subjected to clinical test in a common protocol agreed by PMDA
- Phase 1 studies in healthy male adults (dose finding)
- Phase 2 and 3 in healthy adults (confirmatory trials from age group under 65)
- Safety; clinical laboratory tests, signs and symptoms and physical checkup
- Effectiveness: serum HI antibody, NT antibody
- Comparative analysis of 4 test results with the vaccines produced by the four manufacturers.
-

Accelerated Approval Options/Emergency Use Provisions: H5N1 (including prepandemicprototype vaccines) vaccines have been designated and are subject to priority review , according to the priority review provision of the PALunder PAL. In an emergency, provided that the pre-pandemic/pandemic vaccine is being developed, MHLW will be

granting conditional emergency approval, depending on the extent of the data available at the pointbased on the available data.

In case of emergency at risk of prevalence of disease, such as pandemic situation, where no other effective drug/device available among MHLW approved products in Japan, MHLW will have the authority to give the emergency foreign product approval under PAL to the products which have been approved by relevant foreign authorities upon the abridged NDA application of the foreign manufacturer.

United States of America

Regulatory Authority: Influenza vaccines are regulated by the Food and Drug Administration/Center for Biologics Evaluation and Research/Office of Vaccines Research and Review (OVRR) pursuant to Section 351 of the U.S. Public Health Service Act and specific sections of the U.S. Federal Food, Drug and Cosmetic Act.

Submission Type and Application: The licensing of new biological products, including vaccines, requires the filing of a Biologics License Application and approval is issued only when the review of the BLA shows the product to be "safe, pure and potent". The word potency is interpreted to include effectiveness as demonstrated by adequate and well-controlled clinical studies unless waived as not applicable to the biological product or when an alternative method is adequate to substantiate effectiveness.

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

Timelines: BLA Standard Review: 10 month review (Priority 6 months); CMC Supplement 4 month review

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

Special Requirements regarding Quality and Manufacturing data:

- Description and characterization of drug substance and drug product
- Information regarding methods of manufacturing, including animal sources, virus sources, cellular sources, microbial cells and animal cells (to assess for adventitious agents)
- Assay development/validation
- Process controls, especially for safety processes, such as sterilization and virus clearance
- Manufacturing consistency, including reference standards and release testing
- Drug substance specifications
- Reprocessing
- Container and closure system
- Stability studies
- Composition and characterization of final drug product, including excipients, adjuvants and preservatives
- Specifications and analytical methods for drug product ingredients

Special Requirements regarding Clinical Data:

Original BLA of a manufacturer already licensed by the FDA for the production of annual influenza vaccine where the process for manufacturing the pandemic influenza vaccine is the same:

- clinical trials required to support the appropriate dose and regimen of the pandemic vaccine (based on evaluation of immune response) (immunogenicity)
- assay performance data

- safety data of well-defined local and systemic reactogenicity events
- safety data from six month post-vaccination evaluation (submitted when available).

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

- data from adequate and well-controlled clinical trials establishing a vaccine effect on surrogate endpoints likely to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic or other evidence. Immune response may serve as surrogate endpoint.
- study with adequate power to assess co-primary endpoints-GMT and seroconversion
- Assay performance data
- protocols for post-marketing studies
- safety data as for supplement, described above
- After approval, requirement to study the product further to verify and describe its clinical benefit.

Once a pandemic influenza vaccine against a new influenza subtype has been licensed, further clinical data with a variant of that subtype would likely not be needed for licensure.

Accelerated Approval/ Emergency Use Provisions:

Accelerated Approval of New Biologic Products for Serious or Life-Threatening Illnesses:

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

Emergency Use Authorization (EUA):

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

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

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

determination whether the criteria for issuance of an EUA are met can only be made after an emergency is declared.

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

Investigational New Drug (IND) Use: In accordance with the US Department of Health and Human Services Pandemic Influenza Plan, Supplement 6 Vaccine Distribution and Use, in the event that pandemic spread is rapid and vaccine is needed prior to the completion of the licensure process, state and local health departments should be prepared to distribute unlicensed vaccines under FDA's IND provisions. IND provisions require strict inventory control and record-keeping, completion of a signed consent form from each vaccinee, and mandatory reporting of specified types of adverse events. IND provisions also require approval from Institutional Review Boards (IRBs) in hospitals, health departments, and other vaccine-distribution venues. The FDA regulations permit the use of a national or "central" IRB.

Appendix IB Overview of five selected National Regulatory Authority pathways

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Regulatory Authority	Therapeutic Goods Act, 1989 and Therapeutic Goods Regulations, 1990, Trade Practices Act, 1974 Quarantine Act of 1908	Food and Drugs Act and Regulations Public Safety Act	Directive 2001/83/EC, Article 8 – marketing and authorization application, Regulation (EEC) 726/2004 – submission to the EMEA through centralized procedure.	Pharmaceutical Affairs Law (PAL) (Law 145, 1960 revised 2005) Infectious Diseases Law (revised name 1998)	Section 351 of Public Health Service Act Food, Drug and Cosmetic Act
Submission Type	Category 3 Application	New Drug Submission (NDS): including an On-Site Evaluation	Centralized Procedure (CP) Mutual Recognition Procedure (MRP)	New Drug Application	Biologics License Application (BLA)

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Timelines	Category 3 Application = 45 days after receipt of application	NDS – 300 days standard 180 days for priority	CP – 210 days + EC 30 days, MRP – 210 days (initial national authorization) + 90 days (mutual recognition)	12 months for regulatory timeline (6 months for priority review)	BLA standard review – 10 months, Priority 6 months, CMC Supplement 4 months
Annual Influenza Vaccine Licensure	Full submission required, including quality, pre-clinical and clinical data (in accordance with general CPMP guidance for new vaccines)	Filing of an amendment to the existing license, in which manufacturers submit for review their revised labeling material , any CMC updates pertaining to the new strain and limited clinical data to support tolerablility and immunogenicity	A special Fast Track Type II variation procedure is applicable for annual variation human influenza vaccines.	Manufacturers would submit for review their revised labeling material for the new yearly strain. NCL review the strain changing data.	Submission of a prior approval manufacturing supplement to an existing BLA is required for strain changes (chosen yearly, based on circulating wild-type strains)
Proposed Pandemic Regulatory Pathway	TGA accepts EMEA guidelines on pandemic vaccine licensing.	Submission of an NDS and not an amendment to an existing annual influenza license.	Submission and approval of the pre-pandemic Core Dossier during the inter-pandemic period	Phase I/II & III in 2006, Submission for license and 2007 – Approval of the H5N1 vaccine currently	Submissions for the initial licensure of a pandemic influenza vaccine would be

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
			for evaluation. Once a pandemic is declared a variation to the core pandemic dossier for fast track approval will be submitted.	under development.	submitted as a BLA, which provides for separate trade names and segregation of adverse event reporting. The amount of data a manufacturer would be required to submit with its pandemic influenza vaccine BLA will depend on whether the manufacturer already has a licensed influenza vaccine, and if so, intends to use the same manufacturing process for its pandemic vaccine.

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Pre-Pandemic Vaccine	Licensure is based on approval of a core dossier for a pre-pandemic vaccine with quality, safety and efficacy data provided and authorized during inter-pandemic period.	Pre-pandemic vaccine development: • quality data, • clinical trial applications (CTAs) Pre-Pandemic – CTA for pandemic trial protocols (some as pre-pandemic data)	http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf http://www.emea.eu.int/pdfs/human/vwp/498603en.pdf	Approval is given, based on dossier demonstrating quality, safety and efficacy data during interpandemic period. - Testing protocols and data requirements are addressed in the consultation process of the review agency in collaboration with NCL	See above
Pre-Pandemic Uses	*Same as Europe*	HC must be able to validate productions process, test production capacity and establish minimum standards and requirements for safety and	The core dossier is not be used out of the pandemic context. For vaccines containing avian strains with pandemic potential (such as H5N1), CHMP has adopted a draft Explanatory		

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
		efficacy.	note, identifying dossier requirements. Such avian influenza vaccines for human use must be based (entirely) on the circulation influenza strain against which protection is claimed.		

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Quality and manufacturing requirements	Data obtained in interpandemic period. Same for all uses.	• production and testing of vaccine seed lot manufacturing process and validation • specifications • adjuvant, excipient, container and preservative information • batch analysis • reference standards • stability information • product specific facility information • viral safety info	• vaccine reference virus development and testing, • vaccine seedlots production process etc. • formulation • vaccine standardisation • adjuvant • stability data and protocol	• Control tests for pandemic vaccines on bulk materials; • protein content • sterility • toxicity • inactivation • pH • HA content • thiomersol Aluminum and Formaldehyde content	With adequate controls and characterization, FDA permits use of recombinant or cell culture based technologies in strain production. Either a reassortment or wild type virus.
Clinical data requirement	Data obtained in interpandemic	• challenge studies in	• immunogenicity & safety	• common protocol agreed by PMDA for	<u>Original BLA:</u> See US FDA

National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
s	period Different depending on use; A. Stockpiling for use at beginning of the pandemic B. Use for people at high risk (poultry workers) C. Use as prime and boost population at large Human immunogenicity and safety studies	animals • local tolerance studies • clinical (immunogenicity) studies on healthy adults • targeted studies on vulnerable • protocols for post-market studies, including any necessary informed consent document	• non-clinical safety • novel adjuvant • challenge experiments • human clinical data • formulation • all criteria for annual influenza vaccines • post-authorization commitments	each manufacturer • Phase 1 studies in healthy male adults • Phase 2 and 3 in healthy adults • Safety • Effectiveness; • Comparative analysis	guidance: http://www.fda.gov/cber/gdlns/panfluvac.pdf Dependent upon whether manufacturer currently produces annual influenza vaccine using FDA licensed process and uses same process for the pandemic vaccine..

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National Regulatory Agency	Australia	Canada	European Union	Japan	United States of America
Accelerated Approval/ Emergency Use Provisions	Pandemic Declared –Core Pandemic Dossier using the actual pandemic strain and submit quality/technical data in parallel with product as a pandemic variation to TGA for rapid approval and release.	Licensure of a pandemic vaccine will follow the filing of an NDS containing composite information on the pre-pandemic vaccine supplemented with additional information on the actual pandemic vaccine.	Emergency authorization: • Accelerated review process (max. 150 days +/-) • Conditional marketing authorizations in case of public health crisis	Submission license and approval through priority review process.	• Accelerated Approval of New Biologic Products for Serious or Life-threatening Illnesses, • Emergency Use Authorization (EUA), • Investigational New Drug (IND) Use.
Emergency Use Additional Requirements		• Expedited Review • Notice of Compliance with Conditions • Special Access Programme (SAP) • Interim Orders • Clinical Trials	In case a pandemic occurs before a core dossier is approved: Emergency authorization to be used, relying on very close interaction between the manufacturer and the EMEA using a	Expedited review using available data. Emergency foreign approval scheme may be given to the ones approved in the relevant foreign authorities.	• Accelerated approval of new biologic products for serious or life-threatening illnesses • Emergency Use Authorization (EUA) • Investigational

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

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Appendix II: Regulatory Pathways for Human Pandemic Influenza Vaccine