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**Cadre Réglementaire Européen pour les vaccins
pandémiques en cas d'épidémie de grippe
pandémique**

**(European Regulatory Framework for Pandemic
Vaccines during a Pandemic Influenza Outbreak)**

Falk Ehmann, née 09-X 1976

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Glossary

CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
CTD	Common Technical Document
CHMP / CPMP	Committee for Human Medicinal Products
DG	General Department (European Commission)
EU	European Union
EDQM	European Directorate Quality of Medicines
EPAR	European Public Assessment Report
EMA	European Medicines Agency
ETF	EMA Task Force
EPT	Evaluation Project Team
GMP	Good Manufacturing Practice
GISN	Global Influenza Surveillance Network
HA	Haemagglutinin
ICH	International Committee of Harmonisation
JEIF	Joint EMA Industry Task Force
LAIV	Live Attenuated Influenza Vaccines
MRFG	Mutual Recognition Facilitating Group
MAH	Marketing Authorisation Holder
NA	Neuraminidase
OMCL	Official Medicine Control Laboratory
PSUR	Periodic Safety Update Report
PL	Package Leaflet
QC	Quality Control
RMP	Risk Management Plan
SPC	Summary of Product Characteristics
VEG	Vaccine Expert Group
WHO	World Health Organisation

Executive Summary

In case of an influenza pandemic one of the major responsibilities of public health authorities is to ensure timely supply of human pandemic influenza vaccines. Stringent time requirements for the regulatory authorisation process will have to be met as the relevant strain might become available no sooner than during the first weeks of the pandemic

Two regulatory pathways for the authorisation of pandemic vaccines have been established in the European Union:

- the *Core – Mock-up* and
- the *Prepandemic* principle.

For both pathways products have been granted a marketing authorisation.

The *Core – Mock-up* regulatory pathway involves the submission and approval of a *core pandemic dossier* during the interpandemic period, which is based on a *mock-up vaccine*. Once a pandemic is declared the procedure allows for fast track approval of a pandemic strain variation to supplant the strain in the mock-up vaccine with the final pandemic influenza strain vaccine.

The *Prepandemic* regulatory pathway was developed to cover the possibility that influenza vaccines containing or derived from strains with a pandemic potential (such as H5N1 avian influenza strains) might be used from WHO Phase 3 (see graphic) onwards in an attempt to provide some protection against clinically apparent disease when an actual pandemic strikes.

This document describes these two regulatory pathways in depth referring to guidance developed by the European Medicines Agency (EMA) and its Committee for Human Medicinal Products (CHMP) as intended to provide vaccine manufacturers and pharmaceutical companies advice concerning regulatory pathways for the development of human pandemic influenza vaccines and ensure its most rapid availability in case of a Pandemic.

Introduction

An influenza pandemic is a global outbreak of influenza disease that occurs when a type A influenza strain to which most or all humans are immunologically naïve emerges to cause clinically apparent illness, and then spreads easily from person to person worldwide. Pandemics are different from seasonal outbreaks of influenza, as the latter are caused by subtypes of influenza viruses that are already circulating in the world whereas pandemics are caused by new subtypes or by subtypes that have not circulated among people for a long time.

The greatest priority in case of a potential outbreak of an influenza pandemic is to shorten the time between the emergence of the human influenza virus with a potential for the pandemic and the availability of safe and effective human pandemic influenza vaccines. In this scenario regulatory evaluations to assure the quality, safety and efficacy and requirements for effective postmarketing surveillance of human vaccines that will be used in case of a pandemic influenza outbreak are of major importance.

Besides the important quick availability of an influenza vaccine in case of a pandemic, the amount of available doses after a certain time is of essential importance to cope with an outbreak. Current production of vaccines for novel influenza viruses depends entirely on the manufacturing facilities producing seasonal influenza vaccines. Based on a situation analysis in 2006, potential vaccine supply in case of an influenza pandemic will worldwide fall short by several billion doses. In response to these shortcomings the WHO plan aims to promote increased capacity for production by reaching beyond current seasonal influenza vaccine producers.

Further steps to improve industrial pandemic preparedness range from the construction of new production plants meeting higher biosafety standards, through investigation of antigen sparing technologies (especially adjuvants), to the development of candidate vaccine prototype libraries. Some steps taken to develop a pandemic influenza vaccine are expected to influence seasonal influenza vaccine production. These new approaches may expedite vaccine production at a larger scale in a pandemic situation, making vaccine potentially available weeks before conventional manufacture. In early 2007, 16 manufacturers from 10 countries reported to be developing prototype vaccines against H5N1 avian influenza viruses. Five manufacturers were also involved in the development of vaccines against other avian viruses (H9N2, N5N2, and H5N3). Most manufacturers reported using reference vaccine strains corresponding to viruses provided by WHO Collaborative Centres. More than 40 clinical trials, mostly focusing on healthy adults, had been completed or were ongoing. After completing safety analyses in adults, some manufacturers had initiated clinical trials in the elderly and children. All vaccines tested to date were safe and well tolerated in all age groups. Most of the data

were obtained on healthy adults and further studies in children, the elderly and the immunosuppressed were considered necessary.

A human pandemic influenza vaccine is designed to confer protection against an influenza virus that has the potential to cause an influenza pandemic. Most vaccine immunogenicity data have been generated from the use of egg grown influenza vaccines. Whole virus preparations appear to be more immunogenic than equivalent doses of split vaccine. Alum adjuvanted split vaccines, in striking contrast to some of the more promising alum adjuvanted whole virion vaccines, show modest increases in immunogenicity over unadjuvanted vaccines not allowing significant dose sparing. Some split vaccines formulated with newer adjuvants show encouraging immunogenicity which would likely allow dose sparing. Several manufacturers have established formulations which they believe will meet regulatory requirements. Some studies demonstrate that vaccination with currently available H5N1 prototype vaccines induced a potentially protective immune response against highly pathogenic strains of H5N1 virus isolated at different times and geographical locations. Because of the inherent variability in the assay systems used to measure immune responses, it is unwise to directly compare results from different studies.

The cell culture approach does not rely on fertilized chicken eggs for manufacture allowing for faster (but not infinite) scale-up. Provided that required biosafety levels can be guaranteed, cell cultures offer the potential to work with pandemic influenza strains that would be lethal to eggs without genetic modification. A potential limitation of the cell culture approach is that the process may still require the production of high-yield reassortants. Multiple passage in tissue culture may also introduce cell line specific mutations in the viral genes that can lead to the selection of variants characterized by antigenic and structural changes in the HA protein, potentially resulting in less-efficacious vaccines. Regulatory issues include the presence of potential adventitious agents in mammalian cells and unknown side effects caused by residual host cell and media proteins in combination with new adjuvants (e.g. oil in water emulsions). Some constraints could be overcome by using recombinant DNA technology to produce HA and NA viral antigens in cell culture. These purified antigens would, in turn, be used as the active ingredients in pandemic and/or vaccines for novel influenza viruses.

Live attenuated Influenza Vaccines (LAIV) are not further covered in this document, but a few thoughts shall be reflected here. The technology might be more appropriate for production of a pandemic vaccine because it requires less complex downstream processing than inactivated vaccines. Moreover, this type of vaccine has lower unit cost and production yield likely to be 10 fold higher than inactivated vaccines. In addition, the lower capital investment compared to inactivated vaccines, approximately estimated at US \$ 0.1 per dose, may be attractive for some manufacturers. The use of specific pathogen free (SPF) embryonated chicken eggs is not a regulatory requirement for the

production of LAIV. If SPF eggs were chosen for pandemic influenza vaccine production the egg supply will most likely be insufficient if not at all achievable under a pandemic situation. Unresolved potential public and animal health concerns are associated with live attenuated vaccines for novel influenza viruses. They relate to whether, even if unlikely, shed vaccine virus containing novel antigens could recombine with circulating influenza viruses to become pathogenic and spread to human or animal populations. This type of environmental concern would not exist during a pandemic.

Seasonal human influenza vaccines

Four types of seasonal inactivated influenza vaccine are currently available or have been used extensively in the past:

- a suspension of whole virus particles inactivated by a suitable method,
- a suspension treated so that the virus particles have been partially or completely disrupted by physicochemical means (split vaccine),
- a suspension treated so that the preparation consists predominantly of haemagglutinin and neuraminidase antigens (subunit vaccine),
- a suspension of whole virus particles, split or subunit components formulated with an adjuvant

Whole virion inactivated adjuvanted seasonal influenza vaccine is used in at least one country. Most countries however use split virion or subunit non-adjuvanted inactivated vaccines. While being in general less reactogenic, purified influenza virus surface antigens are less immunogenic than purified whole virion vaccines in immunologically naïve individuals (e.g. small children and persons with no contact to circulating influenza viruses). Individuals with residual immunity display a booster rather than a primary immunization effect after re-vaccination. These observations define the current understanding of split or subunit seasonal influenza vaccines as they must be given on an annual basis to boost the immune system against seasonally circulating strains.

Currently, most companies produce their vaccine(s) by growing the virus in embryonated chicken eggs. Manufacturers are also developing a number of cell culture based technologies to produce subunit seasonal inactivated influenza vaccines. Currently used continuous cell lines include Vero cells which are widely used in manufacturing of other vaccines, the MDCK cell line and others which are less extensively used as a human vaccine substrate.

Further live attenuated seasonal influenza vaccines is used in some immunization programmes. There is preliminary evidence that live attenuated seasonal influenza vaccines produced in embryonated chicken eggs might be more efficacious than un-adjuvanted and inactivated seasonal influenza vaccines.

Interestingly, LAIV have been shown to be more effective in immunologically naïve individuals, i.e. children below two years with no residual immunity towards influenza virus antigens. Efficacy trials in this age group revealed vaccine efficacy (defined as preventing laboratory confirmed influenza infection) exceeding 90% after one dose against influenza virus strains homologous to the vaccine antigens. These findings are in strong contrast to inactivated seasonal influenza vaccines in this age category.

Safety of LAIV in high-risk patients (such as those with asthma, immunocompromised, the very young or elderly people) and data on protection against heterologous virus and minor has to be further investigated.

EMA guidance regarding licensure of vaccines for novel influenza viruses is limited to inactivated vaccines. No guidance exists for LAIV.

Regulatory Framework

Overview

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

Within the European context, there are two regulatory pathways that can be followed depending on the intended use of a vaccine for a novel potential pandemic influenza virus. In one scenario the vaccine for a novel influenza virus although licensed, is not intended to be used or marketed before the pandemic is announced and the exactly matching pandemic strain has to be introduced into the authorization via a fast track type two variation (Core - Mock-up principle).

In the second scenario a vaccine for a novel influenza virus is intended to be used before the pandemic is declared. For this “Prepandemic” vaccine special regulatory provisions apply as described later in this document. Recommendations pertaining to core quality, non-clinical, clinical, and post-marketing specifications, as outlined in EMEA guidance on “Dossier structure and content of Marketing Authorization applications for Influenza vaccines with avian strains with a pandemic potential for use outside of the core dossier context” are agreed as the international expectations for regulatory evaluations of candidate influenza vaccines. Non-clinical and clinical studies conducted in accordance with the requirements of this document should be considered acceptable for the purpose of evaluating candidate vaccines. National regulatory authorities are encouraged to limit requests for additional data to those which are clearly justified to address safety or efficacy concerns unique to that jurisdiction.

Core - Mock-up principle

The EMEA provides guidance for the basis for a fast track authorisation procedure for pandemic influenza vaccines within the EU. The procedure that is further explained below involves the submission and approval of a ***core pandemic dossier*** during the interpandemic period, which is based on a ***mock-up vaccine***. Once a pandemic is declared the procedure allows for fast track approval of a pandemic strain variation to supplant the strain in the mock-up vaccine with the final pandemic influenza strain vaccine.

The core pandemic dossier should describe the quality, non-clinical and clinical data relevant to the mock-up pandemic influenza vaccine. Specific guidance on the scientific content of the quality, safety, efficacy and the Risk Management Plan (RMP) is provided (Guideline on the Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure EMEA/CPMP/4986/03).

The mock-up vaccine should be produced in the same way as is intended for the final (i.e. containing antigen from the actual pandemic strain) pandemic influenza vaccine (e.g. inactivated whole virion, split or subunit vaccine derived from virus grown in cell culture or in embryonated hens' eggs). The antigen content, adjuvant system (if used) and route of administration should also be the same as intended for the final pandemic influenza vaccine.

It is expected that the antigens in the mock-up vaccine should be different from those in the influenza viruses that are circulating, in the inter-pandemic period so that the immunogenicity of the vaccine can be assessed in populations with no or low rates of detectable pre-existing immunity. The core pandemic dossier should contain a justification of the antigens chosen for inclusion in the mock-up vaccine.

The pandemic strain variation application will contain only the quality data that are new and relevant for the pandemic strain. It is not expected that preclinical and clinical data obtained from studies with the final pandemic strain would be included in the pandemic strain variation dossier; Marketing authorisation holders are expected to gather clinical information with the final pandemic strain vaccine as the influenza pandemic progresses.

Responsibilities and distribution of tasks

Different task force groups have been or will be set up to increase the preparedness of both the industry and competent authorities for a possible influenza pandemic.

The Joint EMEA-Industry Task Force (JEIF) consists of CHMP representatives, VEG-experts, Members of the Ad-Hoc Influenza Working Party, Members of the Inspectorate Working Party,

OMCL/EDQM representative(s) involved in the official batch release of influenza vaccines, European Commission representatives (DG Enterprise and DG Sanco), Manufacturers of pandemic influenza vaccines, Representative(s) from WHO, and EMEA staff. The JEIF meets on a regular basis (annually during the interpandemic phase) and provides information and advice to regulatory authorities (EMEA, MRFG, national authorities, Commission services) discusses quality, preclinical and clinical aspects with authorities which are common to all manufacturers, contributes to the development or revision of any additional regulatory guidance in the area of pandemic influenza vaccines and reviews the status of preparedness of vaccine manufacturers

The EMEA Task Force (ETF) consists of Rapporteurs and co-rapporteurs for the core dossier, VEG experts, OMCL representative(s), European Commission representatives (DG Enterprise and DG Sanco) and EMEA staff. This group should be set up in parallel with the submission of the core-pandemic dossier or, at the latest, during the interpandemic period.

The ETF provides information and advice to Regulatory authorities (EMEA, MRFG, National Authorities, Commission services), interacts with the manufacturers, including ongoing scientific discussions prior to the submission of the pandemic variation dossier and discusses post-authorisation data.

The Evaluation Project Team (EPT) consists of Rapporteur and co-rapporteur appointed for the specific dossier and their assessment teams, VEG experts, European commission representative (DG Enterprise) and EMEA Staff and will be set up at the same time of the submission of the core pandemic dossier, and is product specific. The EPT will be involved in the fast track assessment of the pandemic variation.

Core Pandemic dossier

The core pandemic dossier should be submitted in CTD format in accordance with the requirements laid down in the European Commission Notice to Applicants, Volume 2B - Common Technical Document (CTD) together with any other relevant guidelines (i.e. EMEA guideline on “Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application” CPMP/4717/03).

A core pandemic application will be processed through a standard centralised procedure with consultation with its relevant working parties (e.g. the Vaccine Expert Group (VEG)). An opinion from the CPMP will be issued and followed by a European Commission Decision. Clinical data from the current interpandemic influenza strains cannot be used in the core pandemic dossier and manufacturers are required to develop a mock-up vaccine and to test it in clinical trials.

Discussions on the product information (SPC, Labels and PL) will be part of the licensing procedure of the core pandemic dossier. Therefore, during the pandemic variation (see below), the need to updating the product information will be minimal. Finalising the discussion on the product information at the time of the core pandemic dossier authorisation will greatly reduce the time for assessment of

the pandemic variation. The product information approved in the core pandemic dossier authorisation will normally not have to change (except for some information on the pandemic strain) when the pandemic variation is submitted. Once the Commission Decision is issued, the EMEA together with the MAH will prepare a European Public Assessment Report (EPAR) which will be published on the EMEA Website.

This mock-up influenza vaccine may be marketed after a pandemic situation occurs and after a variation application containing all relevant information on the specific pandemic vaccine strain has been filed. Unless the mock-up vaccine strain has the same antigenic composition as the pandemic vaccine strain. In such situation, the mock-up vaccine will be marketed after the announcement of the influenza pandemic. Once the Marketing Authorisation is granted, variations resulting from any changes to the original data submitted i.e. manufacturing changes, maintenance activities, Periodic Safety Updates etc. should be submitted to the EMEA.

Actions taken or to be taken by the national health authorities in the event of an influenza pandemic such as availability and distribution of the vaccine and surveillance are described in National or EU Pandemic Influenza preparedness plans and are not further elaborated in this memoire.

WHO global influenza preparedness plan

Inter-pandemic phase New virus in animals, no human cases	Low risk of human cases	1
	Higher risk of human cases	2
Pandemic alert New virus causes human cases	No or very limited human-to-human transmission	3
	Evidence of increased human-to-human transmission	4
	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

(http://www.who.int/csr/disease/avian_influenza/phase/en/index.html)

As soon as possible after the announcement of a human to human transmission confirmed, the EMEA will organise a JEIF meeting. Issues to be discussed at this meeting include the identification of the manufacturers of pandemic vaccines. This may include a discussion of capacity of production, availability of vaccine reference viruses and reagents, availability of all starting materials for the production of pandemic influenza vaccines (for egg derived vaccines, the availability of fertilised hens' eggs needs to be confirmed), any pending manufacturing issues which would benefit discussion with the authorities, GMP inspection relation issues, status of the authorisation of the core dossier, time lines for submission of pandemic variation, status report on the official release testing of the pandemic influenza vaccine batches: the (draft) OMCL procedure foresees the possibility of official batch release in parallel with QC testing of the final product by the manufacturer. The OMCL will

have to keep the task force informed of the status of individual discussion between the MAH and the OMCL/EDQM and agreement on a plan for the submission of status reports by the MAHs and ongoing scientific discussions with the task force.

WHO intends to distribute vaccine reference viruses as soon as possible. WHO will initiate the work to develop and evaluate candidate strains for the production of vaccines against the novel influenza strains during early Phases. The time manufacturers need to produce a suitable strain will vary from 1 week (if a non pathogenic, antigenically identical, virus strain is available) to 3 months (if reassortants have to be made). Virus strains prepared using reverse genetics can be prepared in circa 3 weeks, but may need 1-2 months of safety testing. Although the official recommendation for composition of the pandemic vaccines will only be made by the WHO / CPMP at the beginning of an outbreak, manufacturers should start the preparation of seed lots from these reference viruses when available.

After the announcement of a pandemic influenza the WHO will announce the antigenic composition of the pandemic influenza strain. It is possible that WHO will also recommend a virus strain representative for the strain causing the pandemic. As soon as possible after this announcement, a CPMP-Ad hoc Influenza working party meeting should be held to recommend the strain to be used for the production of pandemic influenza vaccines for use within the EU. Ideally, the CPMP should publish its strain recommendation within 48 hours of the WHO announcement. This is likely to require a meeting with the influenza specialists in the different EU member states. It is proposed to have an open dialogue with the MAHs during the initial steps of the development and manufacture of the pandemic Influenza vaccine, to allow discussion of critical issues. This dialogue will result in a scientific view from the EMEA Task Force (ETF), facilitating the assessment and the fast-track approval of the pandemic variation. The scientific views of the ETF will be recorded in a 'Task Force Report' which will be provided to the MAH, and which can be attached to the pandemic variation. Therefore, regular task force meetings will be organised with the individual manufacturers during the initial months of the pandemic. The manufacturers indicated that they would need between 9 and 18 weeks to produce the first lots of vaccine. The timeline depends on the need to adapt the virus strain for growth in the different cell substrates. The Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application provides the opportunity to speed up the initial steps of the manufacturing process.

Manufacturers will have received candidate influenza as soon as available thereafter. They have to adapt the vaccine strain to the manufacturing process (if necessary) and will establish and test the seed lots. Vaccine antigen conformity lots will be prepared and tested. During development and manufacture of the conformity lots, the MAH might propose to have (a) meeting(s) with the ETF. Vaccine batches will be prepared and tested by the manufacturers. The official batch release of vaccine batches could be initiated in parallel with release testing by the manufacturers. Practical agreements with the OMCL should be finalised as soon as possible after the announcement of the

influenza pandemic. The MAH will prepare the pandemic variation and submit it to EMEA and the rapporteur/co-rapporteur for evaluation. Manufacturers should inform the EMEA at least 1 week in advance of the anticipated date of submission of the pandemic variation.

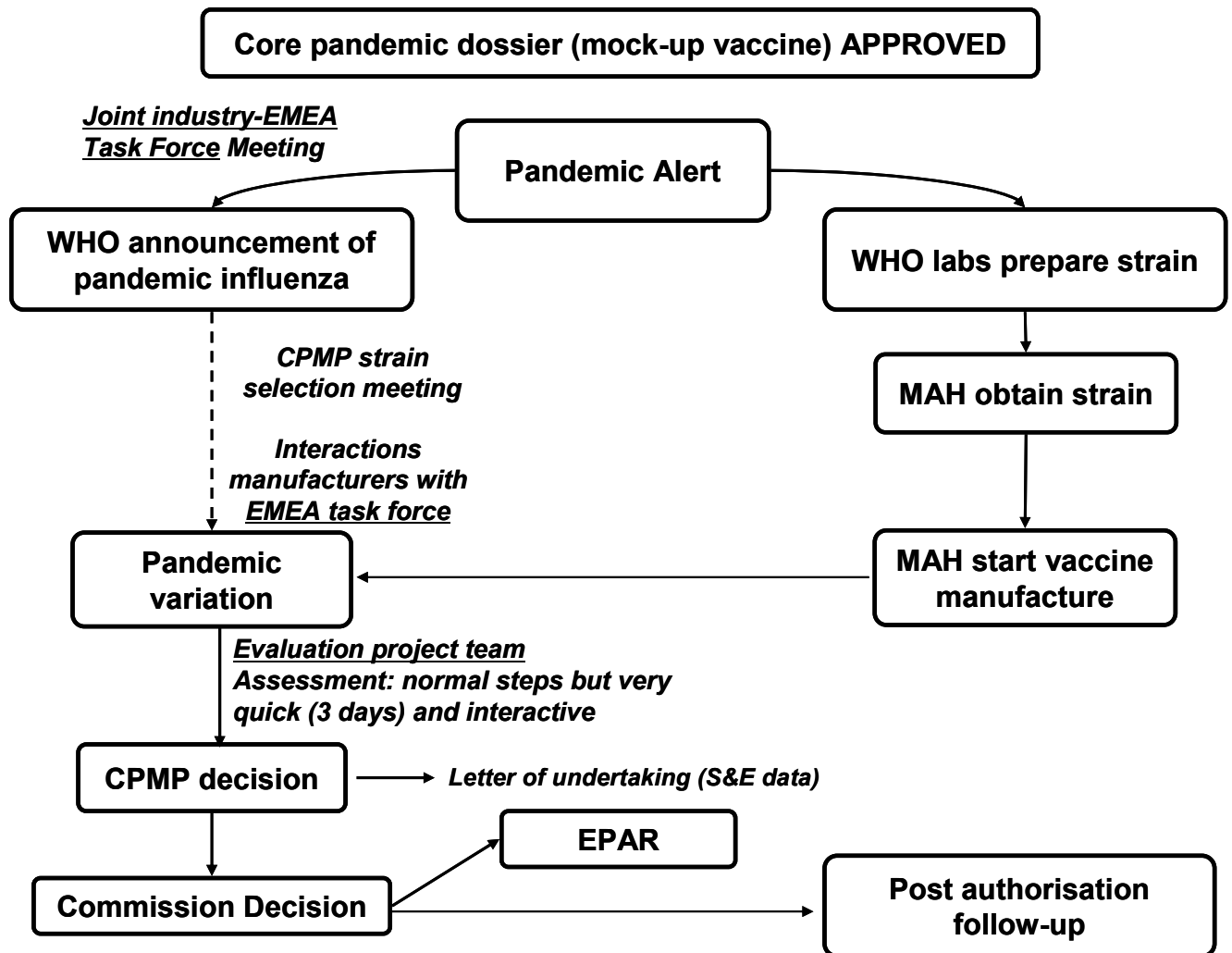
Pandemic variation

The pandemic variation application should be submitted in CTD format in accordance with the requirements lay down in the European Commission Notice to Applicants, Volume 2B - Common Technical Document (CTD) together with any other relevant guidelines.

As soon as the submission time of a pandemic variation is known, the EMEA will organise a meeting of the Evaluation Project Team (EPT) for a fast-track assessment of the submitted variation application.

To ensure a short timeframe a good dialogue with the ETF and critical issues have been discussed in advance of the submission pandemic variation (described above). The intention would be to limit this assessment phase to 2-3 days. The assessment will include all normal steps (assessment report, list of questions, assessment of responses) and will lead to an opinion by the CPMP.

The variation application will not be extensive, as it might not contain non-clinical or clinical data and only those quality data that are specific to the pandemic influenza vaccine. The requirement to submit clinical safety and efficacy data is fulfilled by the commitment of the MAH to collect immunogenicity, effectiveness and safety data of the pandemic vaccine during the actual pandemic and to report these results to the Authorities. The pandemic variation should be similar in size to that of a type II variation application and not a full application. In addition, some of the critical issues might already have been discussed with the ETF.



The EPT meets to agree on strategy and start the assessment of the variation. The company representatives should be available to respond to any issues that might arise during assessment (minor issues for clarification that do not require a formal list of question). If the variation is acceptable the rapporteur/co-rapporteur will prepare their joint assessment report and the EMEA secretariat will prepare an opinion on the Pandemic variation. If the ETP identifies further information to be provided, the MAH is expected to provide the requested data as soon as possible within 24 hours.

If no questions have been raised, the rapporteur/co-rapporteur joint assessment report will be formally agreed by the ETP. If additional information has to be provided by the MAH, this information will be assessed. The company might be asked for further clarifications of minor outstanding issues. The rapporteur/co-rapporteur will prepare their joint final assessment report. The EMEA secretariat will prepare an opinion. The ETP will formally agree on the rapporteur/co-rapporteur joint final assessment report.

The joint assessment report or joint final assessment report, together with the draft opinion, the Letter of Commitment (Commitments relate to quality aspects (if necessary) and to the provision of safety and effectiveness data gathered during use of the vaccine during the Influenza pandemic. A frequent

submission of PSUR data (e.g. monthly) might be requested) from the company and the proposed text for the EPAR update, will be forwarded to the CHMP members. The frequency of PSUR submission during the influenza pandemic needs to be agreed with CHMP prior to approval of the Pandemic variation. Formal adoption by the CPMP should take place within 24 hours. The opinion and assessment report are forwarded to the Commission for the marketing authorisation decision.

The EPAR will be updated immediately after the Commission Decision for the pandemic variation. A template will be developed on the information which need to be provided in the EPAR update after the pandemic variation approval.

Post authorisation / Pharmacovigilance

The pandemic variation will be approved with the commitment to accumulate immunogenicity, effectiveness and safety data of the pandemic vaccine during use.

Facilities for rapid sharing of these data with all EU competent authorities should be in place since the information will likely have implications for all vaccines in use in the pandemic.

If during the initial assessment of these post-authorisation data by the rapporteur and co-rapporteur important signals arise, the ETF (In view of the worldwide implications, it is proposed that also representatives from WHO join the ETF) will meet to consider if this would necessitate changes in the vaccine, in the vaccination schedule or programme.

The advice from the ETF will be forwarded to the CHMP for adoption and an appropriate regulatory action will be taken. This might be the identification of the need for a variation to amend the pandemic marketing authorisation or the product information to be submitted by the MAH, and an expedited review of such a variation might be agreed by the CHMP.

Pre-Pandemic Vaccine

It has become apparent that some EU governments are considering using influenza vaccines prepared from influenza viruses with a pandemic potential (such as H5N1 avian influenza strains).

This section describes the regulatory framework for marketing authorisation applications for influenza vaccines prepared from influenza viruses with a pandemic potential that are intended for use outside of the context of a core dossier. Applications are submitted and evaluated during the inter-pandemic or pandemic alert period and will follow the usual procedures for the authorisation of new vaccines. The indication that results from these applications will allow for use before a pandemic is declared, which will distinguish these Marketing Authorisations from those for mock-up vaccines (i.e. indicated only for use in a declared pandemic; WHO phase 6). In addition, such vaccines could be used in a declared pandemic situation if there are data to indicate that they might be protective (cross protection). This regulatory pathway for a marketing authorisation application is applicable for inactivated influenza vaccines produced from viruses grown in eggs or in cell cultures. It does not address the requirements for development and authorisation of live attenuated influenza vaccines prepared from viruses with the potential to cause a pandemic.

In contrast to the core pandemic dossier that can, in principle, be based on any influenza virus strain to which the study population is immunologically naïve (see Guideline CPMP/VEG/4717/03), the data required in a dossier for marketing authorisation of an influenza vaccine prepared from an influenza virus with a pandemic potential shall all be derived from a vaccine prepared with the strain against which protection is claimed. Any data with other strains that are antigenically similar should be considered to be supportive.

The granting of marketing authorisations for influenza vaccines prepared from influenza viruses with a pandemic potential should not be interpreted as any sort of endorsement of, or recommendation for, the use of such vaccines in the pandemic alert period (WHO phase 3 onwards). Any decisions to recommend the use of these vaccines from WHO Phase 3 onwards are solely the responsibility of individual Governments and their Public Health Authorities.

Non-Clinical

Clinical trials cannot demonstrate protective efficacy of these vaccines. Challenge studies in a relevant animal model can provide evidence regarding the potential protective efficacy of such a vaccine. Ferrets are the preferred animals. These studies should also address the need and role of an adjuvant, if included. Disease markers such as viral shedding, body temperature, body weight loss, behaviour, clinical symptoms as sneezing or nasal rattling, and leukocyte counts are important

endpoints. The vaccine manufacturer should consider the need for intranasal priming of the test animals by infection with a heterologous virus before challenge. Such studies should be conducted using the candidate vaccine and the challenge virus should ideally be the wild type virus from which the vaccine strain is derived. If the use of some wild type strains poses problems of biosecurity the use of an attenuated strain of the homologous virus as the challenge virus could provide useful information.

Clinical

The clinical development of influenza vaccines prepared from a virus with a pandemic potential should in principle be in accordance with the general recommendations regarding the clinical development of vaccines as laid out in the guideline on “Clinical evaluation of New Vaccines” (EMA/CHMP/VEG/164653/05).

Safety

The size of the safety database for each influenza vaccine prepared from a virus with a pandemic potential depending on the population studied will be different. To detect rare ADRs (\leq one in one thousand persons vaccinated) in adults from 18 to 60 years a database of approximately 3000 subject might be sufficient. For specified age groups (e.g. infants, children, adolescents, adults over 60 years of age) the detection of uncommon ADRs resulting in a database of approximately 300 subjects from each specified age group may be sufficient (\leq one in one hundred). For specified risk groups (e.g. immune compromised individuals, chronically ill patients) a database of approximately 300 subjects from each specified risk group might be sufficient (i.e. to detect uncommon ADRs (\leq one in one hundred))

Post-Authorisation issues

At the time of initial authorisation plans should at least be in place to assess antibody persistence, cross-reactivity and cross-protection to new circulating strains. There should also be definite plans for assessment of responses to booster doses in cohorts of vaccinees from each age and risk group for which an indication has been granted. Whenever the opportunity arises, such as during any government-directed use of vaccine within cohorts in individual countries, further information should be collected from observational studies to expand the safety and the immunogenicity database. If there is exposure of vaccinees to circulating influenza strains with a potential to cause a pandemic information on breakthrough cases should be collected. This applies for example to persons dealing with avian influenza outbreaks in flocks or close contacts of documented cases of human infection due to such viruses. It is especially recommended to collect additional data in populations which have been studied to a lesser extent in the pre-authorisation clinical trials.

In the event of a declared pandemic, monitoring the effectiveness of prior administration of any vaccines containing strains expected to provide some protection based on cross-reactivity and/or cross protection studies would be important. If data become available early enough, evidence of protection from prior vaccination could mean that any available pandemic vaccine (i.e. vaccine prepared from the exact influenza strain causing the pandemic) might be directed primarily to previously unvaccinated cohorts. Further such data would be informative for planning future prepandemic vaccination strategies.

If the strategy in any country has been to prime with pre-pandemic vaccine(s) and to administer a dose of pandemic vaccine as soon as it becomes available, then it is recommended that immune responses to the pandemic vaccine should be assessed and compared between any previously vaccinated and unvaccinated cohorts. It may also be possible to monitor the effectiveness of such a strategy provided that the pandemic vaccine can be given early enough to potentially impact on infection rates, complication rates and/or death rates.

Monitoring effectiveness and safety under different scenarios (primed and unprimed population) will be fraught with difficulties and will need careful pre-planning, most likely in close conjunction with public health authorities. Plans should be provided in the Risk Management Plan (RMP).

It is possible that MAHs might wish to propose replacement of the strain in an approved vaccine. This might occur if sequential studies show low or negligible cross-reactivity and crossprotection 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 with different regulatory implications could occur.

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

Another scenario would be the replacement of the strain in the approved vaccine with a different strain of the same subtype (replacing 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.

New Concepts

A new concept of pandemic preparedness could be the add-on of a potential pandemic strain to the seasonal (trivalent) influenza vaccine, resulting in a 4-valent combined seasonal and Pre-Pandemic vaccine. A large portion of the population would be primed on an annual basis and a monovalent 2nd and 3rd dose could be stockpiled or rapidly produced in case of an outbreak. So far no vaccines using this concept have been authorised and no explicit guidance exists but the requirements might be extrapolated from the guidance for seasonal influenza vaccines and the described pre-pandemic ones.

Emergency Regulation

In case of an international influenza pandemic, scenarios under which the EU regulatory system might not be functioning as proposed are possible.

Therefore legislation states that Member States of the Community may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

For this approach Member States shall ensure that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product.

Conclusions

To ensure timely supply of human pandemic influenza vaccines in case of a pandemic, stringent time requirements will have to be met for the regulatory pathway to authorise such vaccines as well as for the identification of vaccine candidate strains, preparation of seed lots, testing and licensing as well as manufacturing and distribution.

Two regulatory pathways for the authorisation of pandemic vaccines have been established in the European Union - the *Core – Mock-up* and the *Prepandemic* principle. For both pathways products have been granted a marketing authorisation.

The *Core – Mock-up* regulatory pathway involves the submission and approval of a *core pandemic dossier* during the interpandemic period, which is based on a *mock-up vaccine*. Once a pandemic is declared the procedure allows for fast track approval of a pandemic strain variation to supplant the strain in the mock-up vaccine with the final pandemic influenza strain vaccine.

The *Prepandemic* regulatory pathway was developed to cover the possibility that influenza vaccines containing or derived from strains with a pandemic potential (such as H5N1 avian influenza strains) might be used from WHO Phase 3 onwards in an attempt to provide some protection against clinically apparent disease when an actual pandemic commenced.

With these two pathways the regulators offer two different concepts for the authorisation of pandemic influenza vaccines. It lies within the responsibility of the member states and public health authorities getting or being prepared for the event of a pandemic in terms of stockpiling, distribution and priming.

Once a pandemic strikes and experience is gained the real efficiency of the vaccines and both regulatory pathways will be demonstrated. Marketing authorisations for pandemic vaccines include Follow-up Measures (FUMs) to ensure that necessary data will be collected to evaluate the vaccines and established pathways during its use.

New concepts like a 4-valent seasonal influenza vaccines containing a potential pandemic strain are under development. Experience for this and other new concepts has still to be gained.

In emergency cases Member States have the possibility to authorise pandemic vaccines. In this case the responsibility for any liability has to be regulated nationally.

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Abstract : Cadre Réglementaire Européen pour les vaccins pandémiques en cas d'épidémie de grippe pandémique

Pour assurer l'approvisionnement en temps voulu de vaccin contre la grippe pandémique humaine en cas de pandémie, des critères de délais rigoureux doivent être respectés par les mécanismes de réglementation en place pour l'autorisation de mise sur le marché de tels vaccins, l'identification de souches candidates pour le vaccin, la constitution d'un lot de semence, ainsi que le testage, l'homologation et également la production et la distribution.

Deux mécanismes réglementaires pour l'autorisation de mise sur le marché de vaccins anti-pandémiques ont été établis au sein de l'Union Européenne, basés sur les concepts de "*pré-dossier – prototype*" et "*pré-pandémique*". Des autorisations de mise sur le marché ont déjà été octroyées dans le cadre respectif de ces deux concepts.

Le mécanisme réglementaire *pré-dossier – prototype* requiert qu'un dossier de type *pré-dossier*, basé sur un vaccin prototype, soit soumis et approuvé pendant la période inter-pandémique. Lorsque qu'une pandémie est déclarée, la procédure permet l'autorisation accélérée d'une variation, remplaçant la souche prototype du vaccin par la souche pandémique, créant ainsi le vaccin antigrippal final.

Le mécanisme réglementaire *pré-pandémique* a été développé pour assurer la possibilité de faire usage de vaccins pandémiques contenant ou dérivé de souches ayant un potentiel pandémique (par exemple la souche de grippe aviaire H5N1), à partir de la phase 3 selon l'OMS, dans le but d'assurer une protection contre une grippe cliniquement observable, lorsqu'une pandémie débute.

Ces deux mécanismes mettent à la disposition des autorités de réglementation deux concepts différents pour la mise sur le marché de vaccins contre la grippe pandémique. La responsabilité incombe aux pays membres et aux autorités de santé publique de se préparer pour une éventuelle pandémie, en termes de stockage, de distribution et de l'administration de la première dose.

Lorsqu'une pandémie est déclarée, l'expérience acquise permettra la démonstration de l'efficacité réelle des vaccins et des deux mécanismes réglementaires. Les autorisations de mise sur le marché des vaccins pandémiques contiennent des FUMs (Follow-up Measures) veillant à ce que les données nécessaires seront recueillies pour permettre l'évaluation des vaccins et des mécanismes en place, lors de leur utilisation.

De nouveaux concepts tels que les vaccins contre la grippe saisonnière quadrivalents, contenant une souche potentiellement pandémique, sont en voie de développement. L'expérience pour ce concept ainsi que pour d'autres nouveaux concepts doit encore être recueillie.

En cas d'urgence, les pays membres ont la possibilité d'octroyer des autorisations de mises sur le marché. Dans ce cas, la responsabilité encourue devra être réglementée au niveau national.