

## 1. GENERAL INTRODUCTION

### 1.1. Procedural issues

This guideline provides the basis for a fast track authorisation procedure for pandemic influenza vaccines within the EU. The procedure that is explained in detail 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 variation as may be necessary to supplant the vaccine virus in the mock-up vaccine with the final pandemic influenza vaccine virus. For more information on the procedure for the fast-track approval of pandemic influenza vaccines, consult the Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03)

This document should be read in conjunction with the relevant Notes for Guidance, monographs of the European Pharmacopoeia (Ph. Eur.) and other guidance documents as listed in section 6. References.

The Core SPC for pandemic influenza vaccines (CHMP/VEG/193031/2004) should be followed.

#### 1.1.1. Core pandemic dossier

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 content of each module of the application is provided in this guideline.

The mock-up vaccine should be produced in the same way as is intended for the final (ie 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

#### 1.1.2. Pandemic variation

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

### 1.2. Legal framework

Directive 2001/83/EC, as amended, lays down in Article 8 the requirements for a marketing authorisation application and Regulation (EC) No 726/2004 lays down the procedure for submission to the EMEA via the centralised route.

Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State and Commission Regulation (EC) 1085/2003/EC of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93. Both Commission Regulations lay

down in Article 8 the requirements for the variation of a marketing authorisation in a pandemic situation with respect to human diseases.

The variation Regulations (EC) 1084/2003 and 1085/2003 will be applicable for any variations to the core pandemic dossier resulting from changes to the original data submitted i.e. manufacturing changes, maintenance activities.

## 2. SCOPE

This Guideline provides guidance on the documentation to be included in the core pandemic dossier and pandemic variation application for inactivated influenza vaccines.

The development and licensing of a live attenuated pandemic influenza vaccine requires additional considerations not covered by this Guideline. Reference is made to the Point to Consider on the development of live attenuated influenza vaccines (EMEA/CPMP/BWP/2289/01) and specific advice should be sought from European competent authorities.

Other vaccine development strategies will be dealt with on a case by case basis and should be discussed with European competent authorities.

This Guideline does not provide guidance on influenza vaccines produced from viruses with the potential to cause a pandemic, for use from WHO Phase 3 onwards<sup>1</sup>.

## 3. QUALITY

As for inter-pandemic influenza vaccines, pandemic influenza vaccines shall be produced in either embryonated hens'eggs or on a cell substrate<sup>2</sup>. Influenza vaccines intended to mimic the pandemic vaccines ("mock-up" vaccines) and the pandemic vaccines themselves shall be compliant with the relevant Ph. Eur. monographs for egg-derived and cell derived inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate. For the testing for freedom from extraneous agents of the seed virus for the pandemic vaccine (viruses, mycoplasma, bacteria and fungi) alternative approaches may have to be taken in view of time constraints.

### 3.1. Core pandemic dossier

#### 3.1.1. Candidate influenza vaccine virus

##### Definition

A candidate influenza vaccine virus ('vaccine virus') is characterised antigenically, genetically and phenotypically and is issued by a WHO Collaborative Centre or by an approved reference laboratory. It is selected to represent an influenza strain that may be considered for mock-up vaccine production. It is the responsibility of the vaccine manufacturer to establish the suitability of the vaccine virus for vaccine production and to establish a vaccine seed lot. Nevertheless, it is recommended that manufacturers consult the competent authority to determine the specific influenza strain subtypes (e.g. H5N1, H9N2 or any other reference virus as indicated below) to be used as a mock-up vaccine virus.

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<sup>1</sup> For this type of influenza vaccines, consult the *Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended to be used outside of the core dossier context* (CHMP/VWP/263499/2006).

<sup>2</sup> If novel cell substrates are used, the applicant will have to provide all necessary characterisation data. See Ph. Eur. General Chapter 5.2.3: Cell substrates for the production of vaccines for human use.

### Vaccine virus

The vaccine virus for the core pandemic dossier is likely to be derived from an avian, porcine or human source by one of the following procedures:

- a) A reassortant virus containing the haemagglutinin (HA) genome segment of a highly pathogenic virus<sup>3</sup>, where the segment has been modified to remove the known determinants of high pathogenicity for avian species, the neuraminidase (NA) segment of the virus and the remaining six segments from an attenuated human influenza virus such as A/PR/8/34 (PR8). The reassortant will be produced by reverse genetics on mammalian cells and may subsequently be grown in eggs or on cells.
- b) A reassortant containing the HA and NA genome segments of an apathogenic virus<sup>2</sup> with some or all of the remaining segments derived from PR8. The reassortant will be produced in eggs or on mammalian cells using either conventional technology or by reverse genetics respectively.
- c) A non-reassortant 'novel' wild-type influenza virus (pathogenic or apathogenic). Appropriate containment for pathogenic viruses will need to be in place (see Annex 2).

### *Examples of vaccine viruses suitable for use as mock-up vaccine virus:*

- H5N1 reassortant derived from a highly pathogenic strain such as A/Hong Kong/213/2003 or A/Viet Nam/1194/2004 by reverse genetics. In view of the occurrence of human H5 virus infections in recent years, this choice has the advantage of being a potential pandemic strain and being produced by reverse genetics, the most likely method of pandemic vaccine virus development.
- H5N3 avian virus. Vaccines produced from the H5N3 strain A/Duck/Singapore/97 have already been tested clinically. This strain is antigenically close to the highly pathogenic H5N1 strain, A/Hong Kong/156/97.
- H9N2 virus. Human H9N2 viruses such as A/Hong Kong/1073/99 have already been used for experimental vaccine production and have been tested clinically. There is preliminary evidence that individuals born before 1968 may have some residual immunity that enhances H9N2 vaccine immunogenicity. Clinical trials of H9N2 vaccines should therefore be stratified by age.
- H2N2 Human virus. A/Singapore/1/57 is the 1957 pandemic strain and has been recently used for experimental vaccine production. Clinical trials of H2N2 vaccine should take account of residual immunity in persons born before 1968.
- H7N1 reassortant derived from a highly pathogenic avian virus by reverse genetics. H7N1 and H7N7 viruses have been associated with European poultry outbreaks in recent years and H7N7 viruses have been associated with human infections.

### Virus quality

The WHO network traditionally develops, in eggs, high yielding influenza vaccine viruses, that are then made available by a WHO Collaborating Laboratory to vaccine manufacturers. Such viruses are either wild-type influenza viruses or reassortants based on PR8. Where the preparation of the vaccine virus involves reverse genetics, there are additional quality considerations beyond those involved with annual vaccine production.

Reverse genetics (options a and possibly b above) requires the use of mammalian cells for development of a vaccine virus and this imposes different requirements to assure the safety and quality of the product. In view of the use of mammalian cells for the development of vaccine virus by reverse genetics, the following minimum set of parameters should be met:

- The cell substrate used to develop the reassortant reference virus has been approved for human vaccine production or should meet the principles of the requirements of Ph. Eur. general chapter 5.2.3. on cell substrates for the production of vaccines for human use.
- Materials used in generating a vaccine virus via reverse genetics process must be compliant with the current version of the Transmissible Spongiform Encephalopathy Note for Guidance.
- Materials used in generating a vaccine virus via reverse genetics process may affect the safety of the vaccine in terms of viral, bacterial, fungal and mycoplasma contamination. Potential safety

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<sup>3</sup> In the context of this Guideline, highly pathogenic and apathogenic refer to the presence or absence of a series of basic amino acid residues at the HA cleavage site that are a known determinant of pathogenicity in avian strains.

risks associated with these materials should be taken into account in the applicant's overall safety evaluation for the vaccine (see 3.1.2. ii).

- Detailed laboratory records are maintained. The laboratory records should include documentation that no other influenza viruses or their genetic material are handled at the same time as the rescue work in order to avoid cross contamination.
- The vaccine virus produced has been assessed by a WHO collaborating laboratory to conclude that antigenic, genetic and phenotypic characteristics make the virus suitable for general use. This includes, when appropriate, testing in animals to demonstrate elimination of high pathogenicity<sup>4</sup> (see also in Non-clinical section).
- A protocol is prepared providing a general description of the vaccine virus development.

#### Safety aspects of the vaccine reference virus

During the development of a mock up vaccine for a core dossier, special consideration must be given to biological containment. Containment issues are outside of the scope of this Guideline. However, some guidance can be found in Annex 1. Manufacturers should adhere to National or Regional Health and Safety regulations.

### **3.1.2. Vaccine seed lots**

#### Production

i) If an attenuated pandemic influenza vaccine virus obtained through an official WHO influenza collaborating centre is further genetically modified for reasons to be justified, it may be necessary to demonstrate maintenance of attenuation by a suitable test in animals, for example the chicken intravenous pathogenicity test, or a pathogenicity test performed with ferrets, depending on the nature of the new genetic change.

ii) A vaccine seed lot system should be employed. The vaccine seed lots may be prepared in SPF embryonated hens' eggs or on a qualified cell line as used for production.

#### Qualification

i) The haemagglutinin and neuraminidase antigens of each seed lot are identified as originating from the correct strain of influenza by suitable methods. Usually, specific antisera obtained from a WHO Collaborating Centre for Influenza are used for determination of HA and NA identity. It is possible that reagents may not be available for the chosen mock-up vaccine, so alternative tests to identify the seed virus (e.g. PCR) should be developed for the mock-up vaccine.

#### ii) Testing for extraneous agents

The vaccine seed virus shall be tested for freedom from extraneous agents (extraneous viruses, bacteria and fungi and mycoplasma) according to the Ph.Eur. monographs for egg-derived inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate. Although the use of reverse genetics is expected to reduce the risk of introducing extraneous agents, it is currently difficult to predict the contribution of reverse genetics derived virus seeds on vaccine quality attributes such as extraneous agent contamination. It remains possible that production cells, reagents and substrates which are derived from animal origin could pose a risk with regard to viral safety. Consequently, whilst the extent of the extraneous risk evaluation for vaccine seed virus originating either from classical or reverse genetics techniques for production of influenza vaccine on cell cultures may be different, such a risk assessment should be made in either case.

iii) Where the influenza seed virus is prepared using reverse genetics, the sequence of the HA and NA genome segment of the influenza virus should be verified and compared to the genome segments of vaccine virus to confirm the genetic stability of the production influenza virus. This should preferably be done at the level of the Working Seed Virus, and at the passage level representing the final vaccine for three batches.

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<sup>4</sup> The virus will be tested for non-pathogenicity in chickens and ferrets according to protocols approved by the OIE ([www.oie.int](http://www.oie.int)) and WHO respectively.

### 3.1.3. Vaccine Production

#### Production

Growth of vaccine virus shall be either in embryonated hens' eggs or on a qualified cell line. Manufacturers using mammalian cell cultures for vaccine production should refer to the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00). Where the production process of the mock pandemic vaccine is based on an established and licensed process, e.g. that for a seasonal influenza vaccine, the process may have to be amended to fulfil the requirements for vaccine production in a pandemic situation. These amendments should be fully explored and validated, as appropriate. The manufacturing development should be detailed in the mock-up MAA.

The European Pharmacopoeia test for abnormal toxicity of the finished product is only required for the validation of the manufacturing process.

#### Formulation

For multidose preparations intended for the pandemic vaccine, an effective antimicrobial preservative should be evaluated<sup>5</sup>, taking into account possible contamination during use and the maximum recommended period after first use (in-use shelf life). Tests for the antimicrobial preservative should be included for the bulk vaccine if appropriate. The applicant should investigate the possible interference of the antimicrobial preservative with other tests.

#### Vaccine standardisation

It is possible that a pandemic vaccine will contain a different quantity of HA than the 15 µg contained in inter-pandemic vaccines.

Normally, influenza vaccine HA content is measured by the immunochemical single radial immunodiffusion (SRD) assay. It is possible that SRD reagents may not be available for the pandemic vaccine, so alternative tests to standardise the vaccine (e.g. protein content, immunogenicity studies in small animals) should be developed and their use validated for the mock-up vaccine. In any case, special emphasis should be placed on accurate determination of low quantities of HA.

#### Adjuvants

It is expected that there will be low rates of detectable pre-existing immunity to the influenza vaccine viruses in the mock-up and final pandemic vaccine. As a result, inclusion of an adjuvant in the formulation may be necessary in order to reduce the amount of antigen needed per dose and/or the number of doses required to elicit presumptively protective immune responses.

For advice on the quality aspects of the adjuvants to be used, consult the CHMP Guideline on Adjuvants in Vaccines for Human Use (EMA/CHMP/VEG/134716/2004). The core dossier should contain detailed information on the origin of starting materials, production process and control testing of the adjuvant. If applicable, special consideration should be given to the control of the extemporaneous mixing of antigen and adjuvant to ensure a consistent preparation.

#### Stability

Stability data for the mock-up vaccine should be developed as described in Ph. Eur monograph of Vaccines for Human Use (2008:0153).

A protocol for testing pandemic vaccine stability should be developed, using data from the mock up vaccine.

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<sup>5</sup> See Ph. Eur. General chapter 5.1.3. Efficacy of antimicrobial preservation and Monograph 0153 Vaccines for human use.

## **3.2. Pandemic variation**

### **3.2.1. Vaccine reference virus**

#### Definition

A reference virus for a pandemic vaccine will be characterised antigenically, genetically and phenotypically and be issued by a WHO Collaborative Centre for Influenza or by an approved reference laboratory. It will be selected to represent an influenza strain recommended by WHO for vaccine production. It is the responsibility of the vaccine manufacturer to establish the suitability of the reference virus for vaccine production and to establish a vaccine seed lot.

#### Reference virus development

The pandemic vaccine reference virus can be derived from avian, porcine or human sources by one of the three procedures specified in section 3.1.1.

In the event that the pandemic virus is highly pathogenic, it will be modified by reverse genetics so that it is no longer pathogenic. Alternatively an apathogenic virus, antigenically equivalent to the pandemic virus may be chosen for vaccine development.

#### Virus quality

The guidance in section 3.1.1. for the mock-up vaccine derived by reverse genetics is equally applicable to the pandemic vaccine viruses.

A pandemic vaccine reference virus will be provided to vaccine manufacturers by one of the WHO Collaborating Centres and, in accordance with CPMP Note for Guidance on harmonisation of requirements for influenza vaccines. The vaccine virus shall be approved by the CHMP.

#### Safety aspects of the vaccine reference virus

Special consideration will have to be given to the biological containment when pandemic influenza vaccines are produced (see Annex 2).

National and Regional Health and Safety regulations must also be observed.

### **3.2.2. Vaccine seed lots**

#### Production

The guidance given for core pandemic dossier also applies to the pandemic variation application. Alternative tests to identify the seed virus (e.g. PCR), developed for the mock-up vaccine, shall be used as long as specific antisera obtained from a WHO Collaborating Centre for Influenza, are not available. When such reagents become available, SRD tests should be used for identity testing.

#### Testing for extraneous agents

The seed virus for production of the pandemic vaccine shall be shown to fulfil the requirements for freedom from extraneous agents (extraneous viruses, bacteria and fungi and mycoplasma) according to the Ph. Eur. monographs for egg-derived inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate. In normal inter-pandemic conditions, the seed virus will not be used for production before the results of such testing are known and compliance has been demonstrated. In a pandemic situation, awaiting the outcome of compendial testing for extraneous agents before starting vaccine production may cause unwanted delays in the availability of vaccine. Therefore a system of parallel testing is recommended: alternative faster tests (e.g. PCR for viruses and mycoplasma, alternative “metabolic” tests or short incubation for bacteria and fungi) can be used to screen the seed virus before use in production and to minimise the chances of rejection of batches due to contaminations; in parallel, the compendial tests can be carried out to demonstrate full compliance of the vaccine.

### **3.2.3. Vaccine production**

#### Production

The guidance given for core pandemic dossier also applies to the pandemic variation application.

The European Pharmacopoeia test for abnormal toxicity of the finished product is only required on the first three batches.

Appropriate immunogenicity data in animals on at least one batch should support the vaccine virus change between the mock up and the pandemic vaccine. Data on at least 3 batches shall be provided after approval of the pandemic variation to demonstrate consistency of production. (see also Non-clinical section)

#### Formulation

In the case an antimicrobial preservative is needed (i.e. for multidose preparations), an assay for the antimicrobial preservative should be included for the bulk vaccine testing.

#### Vaccine standardisation

Depending on the results from the clinical trials with the mock vaccine, a pandemic vaccine may contain a different quantity of HA than the 15 µg contained in the seasonal influenza vaccine.

The alternative tests for vaccine potency, validated for the mock up vaccine, should be used as long as SRD reagents are not available. When SRD reagents become available, they shall be used for potency testing.

#### Adjuvants

The guidance given for core pandemic dossier also applies to the pandemic variation application.

#### Shelf life

Vaccine stability testing is to be performed according to the protocol in the core dossier. Out of specification results are to be reported to the authorities.

## **4. NON-CLINICAL SAFETY AND IMMUNOLOGICAL REQUIREMENTS**

### **4.1. General Considerations**

The protective efficacy of pandemic influenza vaccines can only be evaluated during an actual pandemic situation. While immunogenicity of mock-up vaccines can be assessed in humans the immunological parameters that might correlate with efficacy of a pandemic vaccine are unknown. Therefore, data on immunogenicity and protective efficacy obtained in challenge studies in animals may be used to help assess the potential protective efficacy of a mock-up vaccine and, by implication, of the final pandemic vaccine of the same construct.

The safety of a mock-up vaccine can be assessed in humans and safety data from use of the corresponding final pandemic vaccine can be collected during an actual pandemic. However, there are some safety-related issues that may need to be investigated with the mock-up vaccine in non-clinical studies.

### **4.2. Core pandemic dossier**

#### **4.2.1. Primary Pharmacodynamics (Protection and Immunogenicity)**

##### **4.2.1.1. Proof-of-Concept of Protection**

Challenge studies in a relevant animal model (ferrets are the preferred animals) should provide evidence regarding the potential protective efficacy. These studies should also address the need for and role of the adjuvant, if included. The need for priming with a heterologous virus should be considered and justified.

Challenge should be initially with the homologous vaccine virus. Additional challenge studies using one or more heterologous viruses would provide important information regarding the potential for cross-protection.

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. Immunogenicity data should be obtained during challenge studies in order to evaluate whether any correlation exists between antibody response and development or severity of disease<sup>6</sup>. These key data are expected early during development of the product.

#### **4.2.1.2. Non-clinical immunogenicity**

Immunogenicity data derived from a small animal species that responds well to human influenza vaccine (e.g. chicken, mice, and ferrets) are expected before starting clinical trials. The investigations should include an evaluation of immune responses according to dose and dose interval using the mock up vaccine virus. If an adjuvant is included immunogenicity studies should address the effect and role of the adjuvant, as indicated in the Guideline on Adjuvants (CHMP/VEG/134716/2004).

Immunogenicity studies in animals are also useful to document consistency of production, in particular during the validation phase of a candidate influenza vaccine manufacturing process. Appropriate immunogenicity data for the first three batches of the mock-up vaccine should be included in the application to document consistency of production. Alternatively, these data could be obtained in clinical studies.

#### **4.2.2. Non-clinical safety (Toxicity testing)**

- For split or subunit candidate influenza vaccines that are to be manufactured and formulated similar to the licensed seasonal vaccine (apart from the vaccine virus) or similar to a licensed mock-up vaccine, routine non-clinical toxicity studies need not be repeated, provided that previous studies were performed in accordance with the requirements of the Note for Guidance on preclinical pharmacological and toxicological testing of vaccine (CPMP/SWP/465/95) and were included in the relevant applications.
- Influenza vaccines derived from an entirely new production process or a new formulation will require a complete non-clinical study program as stipulated in the relevant guidelines.
- For new adjuvanting systems applicants should consult the Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004).

In view of the possible use of these vaccines in pregnant women, animal reproductive toxicity studies should be performed and should be available before authorisation. The study design should reflect the clinical dosing schedule (groups with different time points might be considered).

For reduction of, or exemption from, any part of a non-clinical safety investigation program, European competent authorities should be consulted for Scientific Advice.

### **4.3. Pandemic variation**

The only new non-clinical data that need to be submitted are appropriate animal immunogenicity data from at least one batch. Data from at least 3 batches shall be provided after approval of the pandemic variation to demonstrate consistency of production. (see also Quality section).

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<sup>6</sup> A theoretical risk for disease enhancement after administration in naïve subjects was raised for Aluminium adjuvanted candidate vaccines based on a strain of influenza virus not previously used in vaccines.



## 5. CLINICAL REQUIREMENTS

### 5.1. General considerations for the clinical development programme

This section considers:

- The immunogenicity and safety data obtained with the mock-up vaccine that should be included in the core pandemic dossier. Essentially these data will evaluate the administration of a mock-up vaccine that contains (a) influenza virus(es) to which most of all of the population have no detectable immunity.
- Clinical data to be submitted during an actual pandemic, in accordance with the content of the RMP, that are associated with use of the vaccine containing the actual pandemic vaccine virus.

In addition to the guidance provided below, all the relevant sections of the guidance documents, which can be found in Section 6, need to be considered. WHO guidance documents might also be taken into account.

The extent to which the requirements laid down in Guideline on the Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005) have to be fulfilled depends upon several factors. These include the extent to which the manufacturing processes used to produce any mock-up influenza vaccine are shown to be similar to those used to produce one or more licensed inactivated seasonal influenza vaccine.

### 5.2. The Core pandemic dossier and the mock up vaccine

Studies should provide a detailed characterisation of the immunological responses to the mock-up vaccine.

In the pre-submission phase applicants are encouraged to present and discuss the clinical development plan and interim results with European competent authorities. At the time of the marketing authorisation application, the applicants should present final immunogenicity and safety data until 6 months post primary vaccination.

#### 5.2.1. Target population

The data provided in the core pandemic dossier may be obtained solely from healthy adults aged from 18 years, with or without data from subjects aged >60 years.

#### Paediatric data

In a pandemic situation, children may be very vulnerable to infection and so constitute a special target group for vaccination. Therefore, once data have been obtained from adults to support the core pandemic dossier, it is recommended that at least limited data on safety of the mock-up vaccine should be obtained from healthy children<sup>7</sup>. The plan for paediatric studies should be agreed in the Paediatric Investigational Plan (PIP). The results of paediatric trials should be submitted to European competent authorities and, as necessary, may support a variation to the core pandemic dossier.

In the case of an actual pandemic (see section 5.3.4) priority should be given to an assessment of the immunogenicity of the final pandemic vaccine in children. At the time of marketing authorisation the plans for paediatric studies have to be agreed upon in the Risk Management Plan (RMP).

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<sup>7</sup> The paediatric data can also be obtained with the corresponding pre-pandemic vaccine, if submitted in parallel.

### 5.2.2. Design of clinical trials

The clinical development program should be based upon trials that directly compare different dose levels of antigen derived from the candidate influenza vaccine virus(es) for inclusion in the mock-up vaccine.

The primary immunisation schedule, including number of doses and dose intervals, should be justified. If incorporation of an adjuvant is proposed then studies should compare formulations with and without adjuvant and should seek to identify an appropriate antigen-adjuvant ratio.

The numbers of subjects within each clinical trial should be adequate to ensure that the trial is able to fulfil its objectives (see EMEA/CHMP/VWP/164653/2005). Stratification into age categories or into groups with other characteristics that may cause them to respond to the vaccine differently should be employed to ensure that a representative cross-section of the population is studied and sufficient immunogenicity and safety data in each of these strata are presented.

### 5.2.3. Immunological assessment criteria

The primary objective of the immunogenicity studies is to assess whether the mock-up vaccine would likely elicit adequate immune responses, which might be predictive for protection after replacement of the mock-up vaccine virus with the final pandemic influenza vaccine virus.

Depending on the degree of any existing partial immunity in various age groups of the population to the pandemic virus and the virulence of the strain, influenza infections during a pandemic may be expected to:

- Have a different clinical course compared with infections with inter-pandemic strains, with higher rates of complications and mortality.
- Show a different age distribution than is usual during inter-pandemic periods.
- Show a high rate of infectivity.
- Show a waved pattern of incidence.

Due to all the above issues, it is not anticipated that the immunological criteria that are currently applied to the clinical data supplied for the annual vaccine virus change variation procedures for existing inactivated influenza vaccines are relevant to the assessment of potential pandemic vaccines. Literature review and the results of non-clinical data should be used to obtain information on immunological correlates of protection that might be relevant to a pandemic vaccine. Emphasis should be put on full characterisation of the immune response, including those data obtained in preclinical studies.

However, with no other criteria to suggest at present, it is anticipated that mock-up vaccines should at least be able to elicit sufficient immunological responses to meet all three of the current standards set for existing vaccines in adults and older adults >60 years (CPMP/BWP/214/96) based on haemagglutination inhibition (HI)<sup>8</sup> and/or serum radial haemolysis (SRH)

If these criteria are not met the applicants are urged to further support the immune responsiveness of the vaccine using other assays, such as neutralising antibody assays and if possible, explore cell mediated immunity.

It is expected that serum neutralising antibody (SNA) will also be assessed, at least in a subset of vaccinees. In addition applicants are encouraged to measure anti-neuraminidase antibody and to investigate the cell mediated immunity elicited by the mock-up vaccine, although these responses are still of unknown relevance to protection. However exploratory data in a subset of vaccinees after primary and booster vaccination may provide additional insight into the overall effects of vaccination and the potential usefulness of the vaccine (early) in a pandemic.

For HI, SRH and SNA it is recognised that there is considerable intra- and inter-laboratory variation in methodology and that the actual titres that might be reported from a range of samples can be very

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<sup>8</sup> The haemagglutination inhibition determination depends on the assay used (e.g. horse vs turkey erythrocytes).

different. EU regulators are aware that there are efforts ongoing to improve on assay variability and international standards are likely to be developed. It is expected that applicants provide full details of assay validation and controls and that the assays are updated and improved in the light of any new developments and availability of international standards. The applicant is recommended to keep reference serum for future analyses and standardisation.

For all the above assays it is expected that data should be generated against the virus(es) in the mock-up vaccine.

As more data become available during the course of the clinical development programmes with mock-up vaccines the existing immunological acceptance criteria assumed to correlate with protection may need to be redefined. The criteria applied to the total population or to specific target groups may need to be revised and/or entirely new criteria may have to be proposed. The data accumulated may also imply a need to explore different dose ranges and/or different immunisation schedules or may highlight the necessity of using adjuvants. Revisions and proposals for new immunological assessment criteria may be made by applicants and/or by the CHMP. Therefore, companies that are developing mock up vaccines should consult with European competent authorities at regular intervals as may be felt appropriate during the development process.

#### **5.2.4. Vaccination schedule**

Considering the naivety of the population and the use of an inactivated vaccine, a single dose primary regimen is unlikely to be suitable for a pandemic situation. A priming schedule with two (or even more) doses of vaccine may be needed, possibly with incorporation of an adjuvant. Thus in addition to the need to determine the optimal dose of the antigens, alternative schedules relevant for the pandemic situation should be explored. The optimal dose, schedule and interval of dose may depend upon:

- Vaccine specific factors, such as type and amount of antigens and content of any adjuvant
- Population specific factors such as age, immunological naivety to the pandemic strain(s)
- The circumstances of use. For example, the regimen needed to urgently achieve seroprotection when there is already local circulation of virus may be different to that which can be used in less urgent situations (such as when the virus is still confined to other areas or in prophylactic vaccination of special populations such as front line health care workers).

Similar vaccination schedule recommendations for all pandemic influenza vaccines to be licensed are highly desirable in a pandemic situation for practical reasons. However, different schedules may have to be studied and licensed.

#### **5.2.5. Safety**

The safety database for each mock-up vaccine will inevitably be limited due to the reasons acknowledged above. Nevertheless, the database should be sufficient to detect adverse reactions or events at a frequency of approximately 1%. Follow-up for the evaluation of safety should be at least 6 months and should include at a minimum all the local and systemic reactogenicity parameters defined in CHMP/BWP/214/96. If the mock up vaccine contains a novel adjuvant for which there is no or extremely limited supportive data derived from its inclusion at a similar or higher dose in other types of vaccines, then it is necessary to reconsider this minimal requirement. Advice should be sought from EU regulatory authorities.

If any new issues regarding safety arise during the clinical development programme (whether with the mock up vaccines or from reports regarding other similar vaccines), it may be necessary to specifically address these matters in larger pre-pandemic studies.

It is likely that inactivated pandemic vaccines will contain thiomersal. In accordance with CHMP guidance, the level should be kept to the minimum necessary. The applicant should discuss the final thiomersal content of the vaccine.

### 5.2.6. Post-approval commitments

There will be limited immunogenicity and safety data for the mock-up vaccine and protective efficacy data will not be obtained. Also, the final pandemic vaccine will have to be approved without immunogenicity data (see 5.3.1 below). Therefore, as part of the post-approval commitments, applicants should have protocols in place at the time of licensure of the mock-up vaccine to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field. Any post-approval commitment after the declaration of the actual pandemic should be conducted in accordance with the CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine (EMEA/32706/2007)

In addition, immunological investigation should be performed, measuring at least HI and/or SRH and SNA against one or more heterologous strains i.e. drift variants of the mock-up vaccine virus. Due to ongoing drift it is anticipated that these data could be provided on an ongoing basis after initial approval of the core pandemic dossier.

To assess the possible need for revaccination to cover (a) subsequent wave(s) of the pandemic, immune responses should be determined after at least 6 months have elapsed since completion of the primary series in a predefined number of subjects. Follow up data should be collected from at least a relevant subset in which persistence of immunity is evaluated. If applicable (i.e. in case of non-persistent antibodies) responses to booster vaccination should be investigated.

## 5.3. The Pandemic variation and the Final pandemic Vaccine

### 5.3.1. Approval of the Pandemic variation

In the case of an actual pandemic, the vaccination programme would need to be implemented as soon as possible<sup>9</sup>. Provided that the mock-up and final pandemic vaccines are similar other than in vaccine virus and the dose schedule is unchanged, the final pandemic vaccine may be approved for use by means of a variation that addresses only the quality issues and without the provision of clinical data. Clinical safety and efficacy should be studied as described below and the results should be reported to the Competent Authorities after approval of the pandemic vaccine.

In case the final pandemic vaccine deviates from the approved mock-up vaccine in aspects other than the vaccine virus, the Marketing Authorisation Holder (MAH) should seek advice from European Competent Authorities.

### 5.3.2. Post-approval clinical investigations

The MAH should conduct the clinical studies (including a prospective cohort study) as specified in the agreed Pharmacovigilance / Risk Management Plan (see section 5.2.6). This will allow to obtain safety, immunogenicity and efficacy data for the final pandemic vaccines if the situation arises.

The accumulation of immunogenicity, efficacy and safety data should ideally be a co-operative effort between companies and public health authorities<sup>10</sup>. Facilities for the rapid sharing of these data should

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<sup>9</sup> Applicants should also consult the following:

- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03)
- EMEA Pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals (EMEA/198532/2005)

<sup>10</sup> Since several different vaccines are likely to be deployed simultaneously in a pandemic situation without geographical separation of distribution of use, it will likely be possible only to estimate the overall **effectiveness of the vaccination programme**. For the pandemic situation, specific case definitions and case detection definitions should preferably be developed and used consistently. However, these may need to be initiated on an ad hoc basis or may need reconsideration with time as the clinical presentation may change during the late pandemic phase. Protocols should describe the populations to be studied and methods to estimate vaccine

be in place since the information will likely have implications for all the vaccines in use in a single pandemic as well as providing lessons regarding the preparation of intervention strategies for future pandemics. Rapid sharing and rapid review of these data will be important since it may be necessary to implement changes in the vaccine, in the vaccination schedule or programme during the pandemic.

#### **5.3.2.1. Immunogenicity**

Each MAH should perform immunogenicity studies with the final vaccine in all age groups, and in subjects with defined high-risk conditions. Priority should be given to evaluating immunological response in children. To expedite the initiation of such studies, suitable protocols should be in place in advance of any pandemic as well as, if possible, an agreement in principle from investigative sites and ethical committees to conduct such studies.

The early post-vaccination immunogenicity data should be submitted to European Competent Authorities as soon as possible and may require a reconsideration of the posology recommendations.

The subjects enrolled into these studies should be followed carefully for the development of influenza. Data from these subjects should be used to develop possible serological criteria for protection.

As it is likely that different products will be used during the vaccination campaign for the pandemic, it is possible that individuals receiving a two dose primary series will be offered vaccines of different manufacturers. In this case immunogenicity data should allow for subgroup analyses of mixed products schedules.

#### **5.3.2.2. Safety**

Safety data on the final pandemic vaccine will arise from real life use and from post marketing studies as specified in the Pharmacovigilance / Risk management Plan (see 5.3.2). Special attention should be paid to obtaining safety information from groups that will not be represented largely in studies with the mock up vaccine, such as defined high-risk populations and children.

In addition to the assessment of rates of local and systemic reactions in the immediate post-vaccination period, there are specific longer-term and (very) rare adverse events that need to be evaluated, such as the risk of Guillain-Barré syndrome.

For the final pandemic vaccine, large-scale safety data will be generated using the vaccine during a pandemic. Regular PSURs should be submitted to European competent authorities. The frequency and content of the reporting will be agreed with CPMP.

Reporting on adverse events and the period safety update report during a pandemic should follow as far as possible the CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine (EMA/32706/2007)

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effectiveness. Clinical outcomes should at least include age specific morbidity and mortality, including rates of hospitalisation.

## 6. REFERENCES

- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03)
- Core SPC for pandemic influenza vaccines (CHMP/VEG/193031/2004).
- Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended to be used outside of the core dossier context (CHMP/VWP/263499/2006)
- Note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96)
- Cell Culture Inactivated Influenza Vaccines - Annex to note for guidance on harmonisation of requirements for influenza vaccines. (CPMP/BWP/2490/00)
- Points to Consider on the development of live attenuated influenza vaccines (EMEA/CPMP/BWP/2289/01)
- Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004)
- Manual of standards for diagnostic tests and vaccines, 4<sup>th</sup> edition, OIE (2001). Office International des Epizooties, 12 rue de Prony, 75017 Paris, France ([www.oie.int](http://www.oie.int))
- Production of pilot lots of inactivated influenza vaccines from reassortants derived from avian viruses. Interim biosafety risk assessment, WHO Global influenza programme (WHO/CDC/CRS/RMD/2003.5 - November 2003)
- General chapter 5.1.3: Efficacy of antimicrobial preservation; Ph. Eur. 01/2008:50103
- Influenza vaccine (split virion, inactivated); Ph. Eur. 01/2008:0158
- Influenza vaccine (surface antigen, inactivated); Ph. Eur. 01/2008:0869
- Influenza vaccine (surface antigen, inactivated, virosome); Ph. Eur. 01/2008:2053
- Influenza vaccine (whole virion, inactivated); Ph. Eur. 01/2008:0159
- Influenza vaccine (surface antigen, inactivated, prepared in cell cultures); Ph. Eur. 01/2008:2149
- Influenza vaccine (whole virion, inactivated, prepared in cell cultures); Ph. Eur. 01/2008:2308
- Vaccines for human use, Ph. Eur. 01/2008:0153
- Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95)
- CPMP Note for Guidance on the Clinical Evaluation of New Vaccines (CPMP/EWP/463/97).
- CPMP Note for Guidance on the Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
- CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine (EMEA/32706/2007)
- EMEA Pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals (EMEA/198532/2005)

## ANNEX 1

### CONTAINMENT OF THE MOCK-UP VACCINE AND THE PANDEMIC VACCINE

#### Mock-up vaccine

During the development of a mock-up vaccine for a core dossier, special consideration must be given to biological containment, as such novel viruses will not be currently circulating and may pose a threat to human health and the environment. For example, the WHO has developed an 'interim biosafety risk assessment' for production of vaccines from reassortants derived from avian influenza vaccines (ref WHO). This guidance is suitable for reassortants prepared by both conventional techniques and by reverse genetics and for wild type novel influenza viruses. National or Regional Health and Safety regulations must also be observed.

Development of an apathogenic vaccine reference virus from a highly pathogenic virus by reverse genetics will take place at BSL 3+ or 4 containment in the reference laboratory. The virus will then be tested for non-pathogenicity in animals. After successful completion of safety tests, the virus will be released for pilot lot production of the mock vaccine under BSL 2+ containment. Clarification of BSL 2+ containment is provided in the 'WHO interim risk assessment'. As the viruses will be products of genetic modification, their use will also be subject to the Contained Use regulation. This will have implications on environmental safety during vaccine production, but not on final product as the virus will be inactivated at this stage. It is anticipated that mock vaccine production from conventionally derived reassortants and from novel wild type viruses will also take place under BSL 2+ containment.

#### Pandemic vaccine

Development of an apathogenic vaccine reference virus from a highly pathogenic virus by reverse genetics will take place at BSL 3+ or 4 containment in the reference laboratory. The virus will then be tested for non-pathogenicity in animals. After successful completion of safety tests, the virus will be released for pandemic vaccine production. The risk assessment and level of containment for pandemic vaccine production will be reviewed by the WHO after the onset of pandemic influenza activity in the world. National and Regional Health and Safety regulations must also be observed.

新型インフルエンザモックアップワクチンのガイドラインとEMAガイドラインとの比較

EMAガイドライン(原文)	EMAガイドラインの概略	日本ガイドライン(案)	日本ガイドラインの該当箇所	備考(理由等)
<p>GUIDELINE ON INFLUENZA VACCINES PREPARED FROM VIRUSES WITH THE POTENTIAL TO CAUSE A PANDEMIC AND INTENDED FOR USE OUTSIDE OF THE CORE DOSSIER CONTEXT.</p>	<p>パンデミックの原因となりうるウイルスから作成され、承認書の範囲外での使用を意図するインフルエンザワクチンについてのガイドライン</p>	<p>新型インフルエンザモックアップワクチンのガイドライン</p>		
<p><b>EXECUTIVE SUMMARY</b></p> <p>This guideline addresses the quality, non-clinical and clinical dossier requirements for influenza vaccines prepared from viruses with a pandemic potential that are intended for use outside of the context of a core dossier. It also gives guidance on post approval commitments, risk management plans and other post-authorisation activities related to these vaccines.</p> <p>The recommendations in this Guideline are valid for inactivated influenza vaccines prepared from viruses with the potential to cause a pandemic that have been isolated from:</p> <ul style="list-style-type: none"> <li>animals (e.g. avian or porcine strains) or</li> <li>humans (i.e. strains of haemagglutinin (HA) subtypes other than H1 or H3).</li> </ul>	<p>本ガイドラインは、パンデミックの可能性のあるインフルエンザウイルスのワクチンで、承認書の範囲外で使用することを意図しているものについて、品質、非臨床及び臨床データにかかる申請書の要件を記したものである。これらワクチンに関連した承認後のコミットメント、リスク管理、その他の承認後の活動についても記載。</p> <p>本ガイドラインは、以下のようなパンデミックの可能性のあるウイルスから作成される不活化インフルエンザワクチンについて書かれている:</p> <ul style="list-style-type: none"> <li>動物(トリ又はブタ)から分離されたもの</li> <li>人(HA亜型がH1又はH3以外)から分離されたもの</li> </ul>	<p>(日本のガイドライン案にSUMMARYはないが、“1. はじめに”に該当する記載がある。)</p>	-	<p>日本ガイドライン案には、SUMMARYに該当する部分はない。</p>
<p>該当無し</p>	-	<p>1. はじめに 新型インフルエンザ対策行動計画(平成21年2月改定、以下、行動計画)においては、新型インフルエンザの発生後、世界的大流行(以下、パンデミック)に対応するため、ウイルス株が同定されて6ヶ月以内に全国民分のパンデミックワクチンを製造することを目指すこととされている。2010年12月末現在、東アジアから中東・ヨーロッパを中心に強毒型の鳥インフルエンザ(H5N1)が流行しており、ウイルスの変異によりヒトでパンデミックを引き起こす懸念がある。加えて1999年以降、H5亜型以外にも、ヨーロッパや東アジアなどでH7亜型やH9亜型のインフルエンザウイルスのヒトへの感染も数は少ないながらも報告されており、これらの亜型によるパンデミックの可能性も考えられている。</p>	p1L4	<p>日本におけるインフルエンザ流行の動向及びそれへの対策に言及している。</p>
<p><b>1. INTRODUCTION</b></p> <p>The <i>Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation</i> (CPMP/VEG/4717/03) addresses quality, non-clinical and clinical data for core dossiers for the authorisation of mock-up pandemic influenza vaccines. The dossier requirements for such vaccines are based on a mechanism by which it is envisaged that mock-up influenza vaccines would be developed in the pre-pandemic period and then, in an officially declared pandemic situation (WHO Phase 6), the pandemic vaccine would be approved following a variation, which will contain only the quality data specific to strain replacement. The core SPC that was developed for mock-up vaccines and for pandemic influenza vaccines specifically refers to use during a pandemic situation and on the basis of official guidance.</p>	<p>パンデミックインフルエンザのモックアップワクチン承認に必要な品質、非臨床及び臨床データについては、ガイドライン(CPMP/VEG/4717/03)に記載されている。これらワクチンの申請書に関する要件は、モックアップワクチンがプレパンデミック期に開発され、公式なパンデミック宣言後にウイルス株変更に係る品質データのみを含む一変後に承認されることを想定している。モックアップワクチン及びパンデミックインフルエンザワクチンのSPC(製品概要書)では、パンデミック状態において公的な指導の下に使用されることを記載している。</p>	<p>行動計画が目指す短期間で目的とする亜型のパンデミックワクチンを製造するためには、パンデミックの発生前に、ワクチン製造のモデルとなるインフルエンザウイルスを用いたモックアップワクチンを開発し、あらかじめヒトにおける免疫原性及び安全性を確認しておくことで、パンデミック発生時に、モックアップワクチンと同等の製造方法及び品質管理方法に基づいて、パンデミックワクチンを迅速に製造・供給が可能となるよう準備しておくことが重要である。</p>	p1L13	
<p>Since the development of the initial guidance and core SPC 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) outside of the context of a core dossier.</p>	<p>一部のEU加盟国政府では、(H5N1トリインフルエンザ株等の)パンデミックの可能性のあるインフルエンザウイルスから準備したワクチンを、承認書の範囲外で使用することを考慮している。</p>	<p>該当無し</p>	-	<p>EU加盟各国の政府の意向について言及したものの。</p>
<p><b>2. SCOPE</b></p> <p>This guideline is intended for applicants preparing 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 (see sections 4.2 and 4.3).</p>	<p>本ガイドラインの対象となるワクチンの申請は、パンデミック間期又はパンデミック警戒期に提出、評価され、新規ワクチン承認の通常の手順に沿って扱われる。これら申請で承認されたワクチンはパンデミック宣言前にも使用可能であることが、モックアップワクチンの承認と異なる点である(モックアップワクチンはパンデミック宣言-WHOフェーズ6-後にのみ使用可能である)。さらに感染防御効果を示唆するデータが有れば、これらのワクチンはパンデミック期においても使用可能である。</p>	<p>本ガイドラインは、モックアップワクチン及びパンデミックワクチンの製造販売承認申請にあたって提出すべき品質、非臨床及び臨床に関する資料の留意点を示すことを目的としている。製品の特性等によっては、本ガイドラインに示した事項以外に取り得る方策があるかもしれない。必要に応じて、医薬品医療機器総合機構(以下、機構)に相談されたい。</p>	p1L18	



<p>該当無し</p>	<p style="text-align: center;">-</p>	<p>なお、本指針に定める内容以外のモックアップワクチン開発に当たっての基本的な要件や承認申請が必要とされる資料は、通常のワクチン開発と異なるものではなく、「感染症予防ワクチンの非臨床試験ガイドライン」(平成22年5月27日 薬食審査発0527第1号)、「感染症予防ワクチンの臨床試験ガイドライン」(平成22年5月27日 薬食審査発0527第5号)、ICH(日米欧医薬品規制調和国際会議)やWHO(世界保健機構)発出のガイドライン等が参考となる。</p>	<p>p1L22</p>	<p>本邦での薬事申請時に、本ガイドラインとともに参考にするべき他の通知やガイドライン等をあげたものの。</p>
<p>The guideline addresses the content of marketing authorisation applications for inactivated influenza vaccines produced from viruses grown in eggs or in cell cultures.</p> <p>This guideline does not address the requirements for development and authorisation of live attenuated influenza vaccines prepared from viruses with the potential to cause a pandemic.</p>	<p>本ガイドラインは鶏卵又は培養細胞で増殖するウイルスから製造される不活化インフルエンザワクチン申請における記載事項について記したものの。</p> <p>パンデミックの可能性のあるウイルスから作製する弱毒生インフルエンザワクチンの開発と承認のための要件は、記載していない。</p>	<p><b>2. 本ガイドラインの対象範囲</b> 本ガイドラインは、H1亜型あるいはH3亜型以外の インフルエンザウイルス表面の抗原であるHA(ヘムアググチニン)抗原への免疫原性を有し、鶏卵または細胞株から製造した不活化インフルエンザワクチン及び組換えDNA技術を応用した HAワクチンで、皮下または筋肉内接種されるものに適用される。パンデミックワクチン製造時のワクチン製造株については、同一の亜型内の変更だけでなく、異なる亜型の変更も想定している。 生ワクチンについては、パンデミック株の増殖性等の特性により、株変更に伴う免疫原性及び安全性への影響がより顕著となる可能性があるため、本ガイドラインの対象としない。また、HA抗原以外への抗原への免疫原性を期待するワクチンも、免疫原性評価の留意点異なるため、本ガイドラインの対象としない。これらのワクチンの開発を否定するものではなく、開発に当たっては、適宜、機構の対面助言を利用されたい。</p>	<p>p1L29</p>	
<p>It is important to note that 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.</p>	<p>これらワクチンの製造販売承認が、パンデミック警戒期(WHOフェーズ3以降)における使用を裏付けたり推奨するものであると解釈するべきではないと強調する。WHOフェーズ3以降にこれらワクチン使用を推奨する決定は、個々の政府と公衆衛生機関の責任において行われる。</p>	<p>該当無し</p>	<p style="text-align: center;">-</p>	<p>EUの薬事承認制度(中央審査承認方式)に関連した記載。</p>
<p><b>3. LEGAL BASIS</b></p> <p>This guideline has to be read in conjunction with the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.</p>	<p>本ガイドラインはEU指令2001/83付属書 I とともに読まれるべきである。</p>	<p>該当無し</p>	<p style="text-align: center;">-</p>	<p>EMAガイドラインと関係するEU法令についての記述。</p>
<p><b>4. MAIN GUIDELINE TEXT</b></p> <p>It should be noted that, 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.</p>	<p>本ガイドライン対象ワクチンの申請書に記載するデータは全て、防御効果を主張しようとするウイルス株で作製したワクチンに由来するものでなければならぬ。抗原性の類似した他ウイルス株に関するデータであっても有用であると見なすべきである。</p>	<p><b>3. モックアップワクチン開発の基本的考え方</b> モックアップワクチンの開発では、ヒトの間で流行を繰り返していない新規のウイルス株を用い、国民全体もしくは大部分が、パンデミックインフルエンザウイルス株に対して一度も感作されていない(以下、ナイーブ)場合であっても必要な免疫が賦与されるように、抗原性状及び含量、アジュバントの種類及び量、並びに接種経路を設定する必要がある。また、パンデミックウイルス株の特徴によっては、パンデミックワクチンの製造工程におけるパラメータの変更等が必要となる可能性はあるものの、原則として、モックアップワクチンと同等の製造方法及び品質管理方法を設定すべきである。</p>	<p>p2L5</p>	
<p>If an adjuvant is used to elicit a satisfactory immune response in naïve individuals, applicants should follow the Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004).</p>	<p>免疫のない被接種者から十分な免疫反応を引き出すためにアジュバントを使用する場合には、人でのアジュバント使用に関するガイドライン(CHMP/VEG/134716/2004)にしたがうこと。</p>	<p>(アジュバントに関しては、以下に記載: p2L31、p4L23、p6L8)</p>	<p style="text-align: center;">-</p>	<p>日本にはアジュバントに係るガイドラインがない。</p>
<p><b>4.1. Quality requirements</b></p> <p><b>Vaccine reference virus</b></p> <p>The reference virus for vaccine production shall be produced using one of the techniques described in section 3.1.1 of the <i>Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation</i> (CHMP/VEG/4717/03).</p> <p>The choice of strain should be justified by the applicant. For example, reference is made to the WHO document: ‘<i>Antigenic and genetic characteristics of H5N1 viruses and candidate H5N1 vaccine viruses developed for potential use as pre-pandemic vaccines</i>’. It is also the responsibility of the manufacturer to establish the suitability of the reference virus for vaccine production and to establish a vaccine seed lot.</p>	<p>ワクチン製造のための参照ウイルスは、ガイドライン(CHMP/VEG/4717/03)に記載の方法のいずれかにより作製すること。</p> <p>申請者はウイルス株選択の妥当性を説明すること(WHOガイドラインを参照)。参照ウイルスがワクチン製造及びシードロット樹立に適していることの説明も製造者の責任で行うこと。</p>	<p><b>4. モックアップワクチンの製造及び品質</b> モックアップワクチンの製造及び品質に関して検討する際の留意点の例を以下に示す。 ・製造業者がモックアップワクチン製造に使用するウイルス株(以下、モックアップワクチン製造株)を決定する際には、パンデミックインフルエンザウイルス株に対する免疫原性及び安全性を適切に評価できるよう、ヒトにおいて流行を繰り返していない新規ウイルス株(ヒト、豚、鳥などから新たに単離されたウイルスの野生株や遺伝子再集合ウイルス株等)を用いること。</p>	<p>p2L15</p>	

( 4.1. Quality requirements, Vaccine Production, – Vaccine standardisation を参照)	-	・ HAたん白質を主たる標的抗原とするワクチンの場合、標準的なHA含量測定法としてSRD法があるが、パンデミックワクチンの製造・出荷までに、試験実施に必要な抗血清等が得られていない場合も考慮して、HPLC等によるHA含量の測定や、SDS-PAGE等で求めたHA含量率及びたん白質含量を利用したHA含量の算出等の代替測定法をあらかじめ用意し、モックアップワクチンを用いて試験法バリデーション成績を取得すること。	p2L22	
( 4.1. Quality requirements, Vaccine Production, – Formulation を参照)	-	・ パンデミックワクチンとして、マルチドーズバイアルでの使用が想定される場合には、開栓後(初回使用后)の外來性感染性因子による汚染及び安定性を考慮し、保存剤の選択及び添加量並びに開栓後の保存条件(保存時間を含む)を設定する必要がある。原則として、添加される保存剤の量は必要最小量に留めるべきである。	p2L27	
(4. MAIN GUIDELINE TEXT を参照)	-	・ ナイーブな集団に対する効果的な免疫付与や抗原節約の観点も踏まえて、アジュバントの使用も考慮する必要があるが、使用する場合には、アジュバントの品質に関する情報(成分、分量、製造方法及び管理方法等)も申請資料に含めること。	p2L31	
該当無し	-	・ ウイルス株によって不活化条件や精製効率等が異なる可能性を考慮し、モックアップワクチン製造株とは異なる亜型又は同一の亜型でも異なるウイルス株等、複数のウイルス株を用いた検討を行うことにより、各工程の頑健性を確立しておくことが望ましい。	p2L34	
Where the preparation of the vaccine reference virus involves reverse genetics, there are additional quality considerations beyond those involved in seasonal vaccine production. If reverse genetics requires the use of mammalian cells for development of a vaccine reference virus, this would impose additional requirements to assure the safety and quality of the product. The requirements described in section 3.1.1 of the Guideline CHMP/VEG/4717/03 should be met.	細換えDNA技術を用いて参照ウイルスを作製する場合には、季節性インフルエンザワクチン製造に上乗せして品質面で考慮すべき点がある。さらに参照ウイルス作成に哺乳類細胞を使用する場合には、製品の安全性と品質を保證するための追加要件が求められる。ガイドラインCHMP/VEG/4717/03の要件を満たすこと。	・ ウイルスの培養基材として動物細胞株を用いる場合には、腫瘍原性やがん原性を評価すること。また、製造工程における細胞、細胞由来DNA及びたん白質の除去を評価すること。	p2L37	通常の新規ワクチンと同様の要件を満たす必要がある、との前提。 (p1L22)「本指針に定める内容以外のモックアップワクチン開発に当たっての基本的な要件や承認申請で必要とされる資料は、通常のワクチン開発と異なるものではなく…」
Vaccine seed lots - Production A vaccine seed lot system should be employed. The vaccine seed lots may be grown in A19 eggs or on a cell line.	製造:シードロットシステムを採用すべき。ワクチンシードはA19鶏卵又は培養細胞で増やすこと。	該当無し	-	日本ガイドライン案にワクチンシードの製造方法についての記載はないが、通常の新規ワクチンと同様の要件を満たす必要がある、との前提。
- Testing for extraneous agents The seed virus shall be tested for extraneous agents (extraneous viruses, bacteria and fungi and mycoplasma) according to the European Pharmacopoeia (Ph.Eur.) monographs for inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate.	外來性病原体の試験:シードウイルスは、欧州薬局方モノグラフ又はCPMP指針(CPMP/BWP/2490/00)に準拠して外來性病原体(外來性ウイルス、細菌、真菌、マイコプラズマ)の試験を行うこと。	(パンデミックワクチンのウイルスシードの外來性感染性因子については、p6L30を参照)	-	モックアップワクチンのウイルスシードについては、通常の新規ワクチンと同様の要件を満たす必要がある、との前提。

<p><b>Vaccine Production</b></p> <p>- Production Growth of vaccine virus shall be either in embryonated hens' eggs or on a cell line. Manufacturers using mammalian cell cultures for vaccine production should refer to the Ph.Eur. monographs for inactivated influenza vaccines produced in cell cultures and the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00).</p>	<p>製造: ワクチンウイルスは有胚卵又は細胞株のどちらかで増殖させる。哺乳類培養細胞を用いる製造業者は、EPモノグラフ及びCPMP指針を参照すること。</p>	<p>(ウイルスの培養基材については、p2L37を参照)</p>	<p style="text-align: center;">-</p>	
<p>The European Pharmacopoeia test for abnormal toxicity of the finished product is only required for the validation of the manufacturing process.</p>	<p>最終製品のEP異常毒性試験は、製造プロセスのバリデーションにのみ要求される。</p>	<p>該当無し</p>	<p style="text-align: center;">-</p>	<p>モックアップワクチンの品質については、通常の新規ワクチンと同様の要件を満たす必要がある、との前提。</p>
<p>- Formulation For multidose preparations, the need for an effective antimicrobial preservative should be evaluated, taking into account possible contamination during use and the maximum recommended period after first use (in-use shelf life). Tests for the antimicrobial preservative should be included for the bulk vaccine testing, if appropriate. The applicant should investigate the possible interference of the antimicrobial preservative with other tests.  If the candidate influenza vaccine contains Thiomersal as a preservative, the applicant should address the final Thiomersal content of the vaccine, in line with the established CHMP guidance.</p>	<p>組成: マルチドーズの製品では、使用開始後の保存期間におけるコンタミネーションを考慮に入れて、抗菌性保存料の必要性を評価すること。必要に応じてワクチンバルクの試験でも保存料の試験を含めること。保存料が他の試験に影響を及ぼす可能性についても調べること。 保存料としてチメロサルを含む場合には、最終製品での含量を記載すること。</p>	<p>(マルチドーズ製品については、p2L27を参照)</p>	<p style="text-align: center;">-</p>	
<p>- Vaccine standardisation Normally, influenza vaccine HA content is measured by the immunochemical single radial immunodiffusion (SRD) assay. It is possible that adjuvants interfere with these methods: the applicant might develop and validate alternative tests to standardise the vaccine (e.g. protein content, immunogenicity studies in small animals).</p>	<p>ワクチンの標準化: 通常、ワクチンのHA含量はSRD法により測定される。アジュバントが測定法に干渉する場合には、申請者が試験法を開発しバリデートすること(例えば、タンパク質含量、小動物を用いた免疫原性試験など)。</p>	<p>(ワクチンの標準化については、p2L22を参照)</p>	<p style="text-align: center;">-</p>	
<p>- Stability Stability data for the candidate influenza vaccine should be developed as described in Ph. Eur monograph of Vaccines for Human Use (Q153). A minimum of 6 months real time stability data need to be included in the application.  Vaccine components (e.g. bulk antigen and adjuvant) might be stored separately.  If the marketing authorisation holder wants to extend the shelf life, non-clinical and/or clinical investigation might be considered necessary and the testing program should be discussed with the competent authorities.</p>	<p>安定性: インフルエンザワクチン候補薬の安定性試験は、EPモノグラフに記載に沿って行うべきである。申請時には最低限6ヶ月の安定性実試験データが必要である。  ワクチンの各成分(バルク抗原やアジュバント)は、別々に保管することも可能。  有効期間を延長する場合には、非臨床、臨床試験が必要と考えられ、試験プログラムが担当機関で検討される必要がある。</p>	<p>(パンデミックワクチンの安定性試験については、p7L4を参照)</p>	<p style="text-align: center;">-</p>	<p>モックアップワクチンの安定性試験については、通常の新規ワクチンと同様の要件を満たす必要がある、との前提。</p>
<p>該当無し</p>	<p style="text-align: center;">-</p>	<p>・ 製造販売承認申請書の記載方法は、通常の医薬品と同じである。原薬や製剤の品質管理試験の規格値は、モックアップワクチンで得られた成績を踏まえて記載すること。  各モックアップワクチンの特性や製造方法等に応じて、上記以外にも留意すべき事項があるかもしれない。必要に応じて機構に相談されたい。</p>	<p style="text-align: center;">p3L1</p>	<p>本邦での製造販売承認申請書の記載要領について述べたもの。</p>
<p>該当無し</p>	<p style="text-align: center;">-</p>	<p>5. モックアップワクチンの非臨床試験 モックアップワクチンの非臨床試験については、「感染症予防ワクチンの非臨床試験ガイドライン」(平成22年5月27日 薬食審査発0527第1号)の他、以下の点に留意することが必要である。</p>	<p style="text-align: center;">p3L8</p>	<p>本邦で参考にすべきガイドラインをあげたもの。</p>

<p><b>4.2. Non-clinical testing requirements</b></p> <p><b>4.2.1 Primary Pharmacodynamics (Protection and Immunogenicity)</b></p> <p><b>4.2.1.1 Proof-of-Concept of Protection</b></p> <p>The protective efficacy of the vaccines that are the subject of this guideline cannot be established in clinical trials. Therefore, contributing to a weight-of-evidence approach, challenge studies in a relevant animal model (ferrets are the preferred animals) can provide evidence regarding the potential protective efficacy of such a vaccine. These studies should also address the need and role of the 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 applicant should consider the need for intranasal priming of the test animals by infection with a heterologous virus before challenge.</p>	<p>本ガイドラインの対象となるワクチンの感染防御能は、臨床試験で確認できない。したがって適切な動物モデル(フェレットが望ましい)によって、このようなワクチンの感染防御能に関する根拠データを得ること。アジュバントを使用する場合には、これら試験でその必要性についても検討すること。ウイルス産生、体温、体重減少、行動、臨床兆候(くしゃみ、鼻づまり)、白血球数などがエンドポイントとなる。攻撃試験では、ワクチン株とは別株を試験前に予め経鼻感染することについて考慮すること。</p>	<p><b>5.1. 発症予防効果の評価</b></p> <p>パンデミックワクチン開発時には、実際のパンデミックインフルエンザは発生していないことから、ヒトでの発症予防効果の検討は困難である。したがって、モックアップワクチン及びモックアップワクチン製造株を適切な動物モデル(フェレット等)に接種する攻撃試験により、発症予防効果を評価することが重要である。攻撃試験の成績から得られた発症予防効果と免疫反応との関係に基づき、臨床試験における免疫学的評価指標を設定することも考えられる。</p> <p>組換えDNA技術を応用したHAたん白質やその一部分を標的抗原とするワクチンは、季節性インフルエンザワクチンを含め、世界的にも使用実績が乏しく、HAたん白質の糖鎖構造の違い等により十分な予防効果が期待できない可能性も考えられることから、動物を用いた発症予防効果の評価は十分に行う必要がある。</p> <ul style="list-style-type: none"> <li>・攻撃試験においては、発症予防効果及び抗体産生等の免疫反応について十分評価する必要があるが、その際には、モックアップワクチン製造株と異なるウイルス株に対する交差免疫についても十分に検討すること。</li> <li>・亜型が異なる株によるパンデミック発生も想定し、可能な限り、異なる亜型を用いて製造したワクチンについて、あらかじめ攻撃試験による発症予防効果を評価しておくこと。</li> <li>・アジュバントの必要性についても検討することが望ましい。</li> </ul>	<p>p3L13</p>	
<p>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. It is recognised that use of some wildtype strains poses problems of biosecurity in performing these studies; however, use of an attenuated strain of the homologous virus as the challenge virus will provide useful information.</p> <p>The candidate vaccine is likely to be a specific strain within a heterogeneous group of viruses of pandemic potential. It is therefore of interest to examine cross-protection of the vaccine against other strains and such studies should be considered. Data on cross-protection could derive from challenge or serological studies using heterologous viruses. Such studies are a useful adjunct to the data demonstrating the efficacy of the vaccine. Data deriving from studies with heterologous viruses will be required if cross-protection (against different strains of the same subtype) in humans is claimed (see also section 4.3 - Induction of immunity to other influenza strains).</p>	<p>攻撃試験はワクチン候補薬を用いて実施すべきであり、攻撃ウイルスは理想的にはワクチン株の元になった野性株を用いるべきである。野性株を用いた試験がバイオセキュリティ上の問題となる場合には、同じウイルスの弱毒株を攻撃試験に用いても有益な情報が得られる。</p> <p>候補ワクチンは、パンデミックの可能性のあるヘテロなウイルス集団の中の特定の株となることが予想される。そのため他株への交差反応性を調べることは重要であり、そのような試験を実施すべきである。交差反応性のデータは他ウイルス株を用いた攻撃試験または血清学的試験から得られる。同じ亜型の別株への交差反応性を主張するのであれば、他株を用いた試験が必要である。</p>	<p>(攻撃試験については、p3L23を参照)</p>	<p>-</p>	
<p>The concern that influenza vaccines could induce disease enhancement (as reported with inactivated adjuvanted measles and respiratory syncytial virus vaccines in the 1960's) may be investigated using suitable endpoints in the immunisation and challenge studies.</p>	<p>インフルエンザワクチンがdisease enhancement(アジュバントを含有する不活化麻疹及びRSVワクチンで1960年代に報告された)を引き起こす懸念について、免疫試験及び攻撃試験で適切なエンドポイントを設定して調べる必要があるかもしれない。</p>	<p>該当無し</p>	<p>-</p>	<p>非臨床試験については他のガイドラインを参照することとしている。</p> <p>(p3L9)モックアップワクチンの非臨床試験については、「感染症予防ワクチンの非臨床試験ガイドライン」(平成22年5月27日 薬食審査発0527第1号)の他、以下の点に留意することが必要である。</p>
<p>If the applicant submits data from challenge studies performed with mock-up pandemic vaccines or other influenza vaccines prepared from viruses with a pandemic potential, the relevance of the findings to the candidate vaccine should be justified.</p>	<p>モックアップパンデミックワクチン又はパンデミックの可能性のある他のインフルエンザウイルスで実施した攻撃試験のデータを提出する場合には、試験成績とワクチン候補薬と関連性について説明する必要がある。</p>	<p>(攻撃試験については、p3L13を参照)</p>	<p>-</p>	
<p><b>4.2.1.2 Non-clinical immunogenicity</b></p> <p>Immunogenicity data derived from a small animal species that respond well to human influenza vaccine (e.g. ferrets and mice) are expected before starting clinical trials. The investigations should include an evaluation of immune responses according to dose and dose interval using vaccine that contains the strain intended for the final product. If an adjuvant is included, immunogenicity studies should address the need, the specific identity and role of the adjuvant, as indicated in the Guideline on Adjuvants (CHMP/VEG/134716/2004)</p>	<p>臨床試験の開始前にヒトインフルエンザワクチンによく反応する小動物(フェレット及びマウス)を用いた、免疫原性試験の実施が望ましい。最終製品で用いようとするウイルス株のワクチンを使用して、用量及び投与間隔に係る免疫反応を評価すること。アジュバントを使用する場合、ガイドライン(CHMP/VEG/134716/2004)に沿ってアジュバントの必要性、特性、役割について記述すること。</p>	<p><b>5.2. 免疫原性評価</b></p> <ul style="list-style-type: none"> <li>・ヒトインフルエンザワクチンへの反応性が良いマウス、フェレット等の動物を用いた免疫原性評価により、投与量、投与回数、投与経路、アジュバントの必要性について臨床試験開始前に検討しておくこと。</li> </ul>	<p>p3L30</p>	