## BULK VACCINE

Date of test:.....

Test results:.....

**1. Information on manufacture**

Name and address of manufacturer:.....

1.1 Lot number:.....

1.2 Lot number and volume of monovalent pools used to prepare bulk:.....

.....

1.3 Other substances added and volumes:.....

.....

1.4 Date of blending:.....

**2. Tests on bulk vaccine**

Analytical tests

Method(s):.....

Test results:.....

(include test for mercury, if appropriate)

## FINISHED PRODUCT

### 1. Information on manufacture

Name and address of manufacturer:.....

1.1 Lot number:.....

1.2 Date of filling:.....

1.3 Type of container:.....

1.4 Volume in container:.....

1.5 Number of doses filled:.....

### 2. Tests on finished product

2.1 Identity for haemagglutinin

Method:.....

Date of test:.....

Test results:.....

2.2 Sterility

Method:.....

Date of test:.....

Test results:.....

2.3 Haemagglutinin antigen content

Method:.....

Date of test:.....

Test results:.....

2.4 Total protein (this test may be performed on bulk vaccine)

Method:.....

Date of test:.....

Test results:.....

2.5 Abnormal toxicity

Method:.....

Date of test:.....

Test results:.....

2.6 Ovalbumin (this test may be performed on bulk vaccine)

Method:.....

Date of test:.....

Test results:.....

2.7 Endotoxin

Method: .....

(e.g. type of limulus kit)

Date of test:.....

Test results:.....

2.8 pH

Date of test:.....

Test results:.....

2.9 Preservative content

Method:.....

Date of test:.....

Test results:.....

2.10 Appearance:.....

# E. CLINICAL TRIALS RELATED TO YEARLY LICENSING OF INFLUENZA VACCINE

## 1. INTRODUCTION

When a new application for marketing authorisation for an influenza vaccine is made, full clinical trial data should be submitted with the application. Such clinical trials are outside the scope of this note for guidance. However, the strain composition of influenza vaccines is modified periodically to take account of the changes in the prevalent viruses causing influenza and manufacturers should apply for yearly licensing to accommodate strain changes.

Vaccine manufacturers are required to be involved in ongoing clinical trials of influenza vaccines and to present the results to the competent authorities. Guidance for performing these clinical trials is given in this section.

The purpose of such trials is to verify:

- the tolerance or incidence of adverse reactions;
- the immunogenicity of the hemagglutinin of the vaccine strains, i.e. the titre and frequency of anti-HA antibody responses;

Whenever the characteristics of a new strain incorporated into the vaccine or the susceptibility of the population to the new strain requires adjustment of the doses, manufacturers may be advised to test various doses of antigens to confirm the adequacy of 15 μg HA per strain and per dose.

The yearly clinical trials on influenza vaccine shall be carried out in accordance with Good Clinical Practice for Trials on Medicinal Products in the European Community.

This information will be submitted at the time of yearly licensing and should include satisfactory evidence of immunogenicity and safety before a licence is granted.

## 2. GENERAL REQUIREMENTS

### 2.1 Vaccine used in the trial

The composition of the vaccine used in the trial shall be such as to fulfill the requirements of the yearly EEC recommendation with regard to vaccine strains. The batches of vaccine used shall be representative of the product placed on the market.

### 2.2 Trial population

The tolerance and efficacy of the vaccine shall be evaluated separately in two groups of healthy volunteers, aged between 18 and 60 and over 60; for the latter group, it is important that the previous vaccination status of each subject be known and recorded. Volunteers receiving influenza vaccine within the previous 6 months should be excluded because they may compromise assessment of vaccine immunogenicity.

Groups of at least 50 individuals shall be constituted.

## 2.3 Trial procedure

a) Just prior to vaccination, a 10 ml venous blood sample shall be taken from each trial subject, for base-line titration of circulating anti-HA antibodies;

b) Immediately thereafter, each subject shall receive 1 dose of vaccine (0.5 ml) by intramuscular or subcutaneous injection into the upper arm. The injection shall be given into the opposite arm from which blood was drawn;

c) approximately 3 weeks after vaccination, a 10 ml blood sample shall be taken from each subject. Sera shall be separated and stored at -20°C; samples shall be kept at the disposal of the control laboratories for epidemiological studies and possible further antibody titration;

d) in the event of intercurrent infection, nasal and/or pharyngeal swabs shall be collected, in order to allow diagnosis of either influenza or another viral respiratory infection.

## 2.4 Monitoring of adverse reactions

a) Trial subjects shall receive, at the time of vaccination, a standardised form to complete and give to the investigator when they come for the post-vaccination blood sampling;

b) the form shall allow for collection of the following information:

- initials of the subject, with date or year of birth;
- previous anti-influenza vaccinations and previous adverse reactions, if any;
- previous influenza infections, with date, description of symptoms and virological confirmation, if any;
- adverse reactions for the 3 days following vaccination, either local (induration, erythema, ecchymosis, pain) or general (fever, shivering, malaise, other side-effects);
- other adverse reactions lasting 2 days beyond vaccination should be noted.

## 2.5 Antibody titration

All sera shall be assayed for anti-hemagglutinin antibody against the prototype strains by HI (Palmer et al., 1975) or SRH (Schild et al., 1975, Aymard et al., 1980) tests.

Positive and negative sera as well as reference preparations may be obtained from a reference laboratory.

## 2.6 Interpretation of results and statistics

Antibody titrations shall be done in duplicate; pre- and post-vaccination sera shall be titrated simultaneously.

The titre assigned to each sample shall be the geometric mean of two independent determinations:

a) for the purposes of calculation, any HI result < 10 (= undetectable) shall be expressed as 5 and any negative SRH result shall be expressed as 4 $mm^2$(*);

b) in HI tests, seroconversion corresponds to:

- negative prevaccination serum / postvaccination serum ≥, 40;
- a significant increase in antibody titre, i.e. at least a fourfold increase in titre;

c) in SRH tests, seroconversion corresponds to: (*)

- negative prevaccination serum / postvaccination serum: area ≥, 25 $mm^2$;
- a significant increase in antibody titre, i.e. at least a 50% increase in area;

d) statistical parameters to be determined:

- geometric mean of prevaccination serum anti-HA antibody titres;
- increase in the geometric mean of antibody titre;
- number of seroconversions;
- proportion of subjects with a titre of antibodies before vaccination;
- proportion of subjects with a titre of antibodies after vaccination;

e) clinical tolerance: frequency, mean time of appearance and duration of all local and general side-effects shall be calculated.

Interpretation of results should take into account the route of administration and any recent history of influenza immunisation or infection.

## 3. CRITERIA FOR ASSESSMENT OF VACCINES

### 3.1. Serological data

a) the following serological assessments should be considered for each strain in adult subjects, aged between 18 and 60, and at least one of the assessments should meet the indicated requirements :

- number of seroconversions or significant increase in antihaemagglutinin antibody titre > 40%;
- mean geometric increase > 2.5;
- the proportion of subjects achieving an HI titre ≥40 or SRH titre >25 $mm^2$ (*) should be > 70%.

b) the following serological assessments should be considered for each strain in adult subjects aged over 60, and at least one of the assessments should meet the indicated

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* In most SRH test systems, a zone area of 25 $mm^2$ is approximately equivalent to an HI titre of 1:40 (Wood et al, 1994). However, this relationship can be affected by experimental conditions and should be reexamined in each laboratory so as to calibrate the test system adequately.

requirements:

- number of seroconversions or significant increase in antihaemagglutinin antibody titre > 30%;
- mean geometric increase > 2.0;
- the proportion of subjects achieving an HI titre ≥40 or SRH titre ≥25 $mm^2$ (*) should be > 60%.

### 3.2. Clinical data

The frequency of the following symptoms should be assessed:

a) local reactions:

- indurations larger than 50 mm diameter and persisting for more than 3 days;
- ecchymosis;

b) general symptoms:

- temperature above $38^0C$ for 24 hours or more;
- malaise;
- shivering.

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* In most SRH test systems, a zone area of 25 $mm^2$ is approximately equivalent to an HI titre of 1:40 (Wood et al, 1994). However, this relationship can be affected by experimental conditions and should be reexamined in each laboratory so as to calibrate the test system adequately.

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**COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)**

# GUIDELINE ON INFLUENZA VACCINES PREPARED FROM VIRUSES WITH THE POTENTIAL TO CAUSE A PANDEMIC AND INTENDED FOR USE OUTSIDE OF THE CORE DOSSIER CONTEXT.

| | |
|---|---|
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| | |
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| **KEYWORDS** | Pandemic influenza vaccines for human use; Strains with pandemic potential; Quality, Non-clinical and Clinical requirements |



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**GUIDELINE ON INFLUENZA VACCINES PRODUCED FROM VIRUSES WITH THE POTENTIAL TO CAUSE A PANDEMIC AND INTENDED FOR USE OUTSIDE OF THE CORE DOSSIER CONTEXT.**

## TABLE OF CONTENTS

## EXECUTIVE SUMMARY

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.

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:

- animals (e.g. avian or porcine strains) or
- humans (i.e. strains of haemagglutin (HA) subtypes other than H1 or H3).

## 1. INTRODUCTION

The *Note for Guidance on dossier st ructure and content for pandemi c influenza vaccine marketing authorisation (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.

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.

## 2. SCOPE

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).

The guideline addresses the content of marketing authorisation applications for inactivated influenza vaccines produced from viruses grown in eggs or in cell cultures.

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.

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.

## 3. LEGAL BASIS

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.

## 4. MAIN GUIDELINE TEXT

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.

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).

### *4.1. Quality requirements*

**Vaccine reference virus**

The reference virus for vaccine production shall be produced using one of the techniques described in section 3.1.1 of the *Note for Guidanc e on dossier structure and content f or pandemic influenza vaccine marketing authorisation* (CHMP/VEG/4717/03).

The choice of strain should be justified by the applicant. For example, reference is made to the WHO document: '*Antigenic and genetic characteristics of H5N1 viruses and candidate H5N1 vaccine viruses developed for potential use as pre-pandemic vaccines*'[1]. 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.

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.

**Vaccine seed lots**

- Production

A vaccine seed lot system should be employed. The vaccine seed lots may be grown in embryonated hens' eggs or on a cell line.

- 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[2] or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate.

**Vaccine Production**

- 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).

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[1] http://www.who.int/csr/disease/avian_influenza/guidelines/recommendationvaccine.pdf

[2] See following Ph. Eur. monographs on inactivated influenza vaccines: 0158 ; 0159 ; 0869 ; 2053; 2149 ; 2308.

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, the need for an effective antimicrobial preservative should be evaluated[3], 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.

- 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).

- Stability

Stability data for the candidate influenza vaccine should be developed as described in Ph. Eur monograph of Vaccines for Human Use (0153). 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.

## *4.2. Non-clinical testing requirements*

### 4.2.1 Primary Pharmacodynamics (Protection and Immunogenicity)

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

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.

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 wild

[3] See Ph. Eur. General chapter 5.1.3. Efficacy of antimicrobial preservation and Monograph 0153 on Vaccines for human use.

type 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.

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).

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.

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.

*4.2.1.2 Non-clinical immunogenicity*

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)

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. Immunogenicity data for the first three batches should be included in the application to document consistency of production.

**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 strain) or similar to a licensed mock-up vaccine, routine non-clinical toxicity studies need not be repeated, provided that they have been performed in accordance with the requirements of the Note for Guidance on preclinical pharmacological and toxicological testing of vaccine (CPMP/SWP/465/95) and have been included previously in the relevant applications.

- In the 1960's, enhanced disease was reported in predisposed infants vaccinated with inactivated aluminium-adjuvanted Respiratory Syncytial Virus Vaccine and Measles Virus Vaccine, following subsequent natural infection with the respective viruses. From the literature there is evidence that the disease enhancement, first seen in humans, has been repeated in animal models using a variety of antigens and adjuvants. Therefore, a similar - albeit theoretical - concern was raised for whole virus and split inactivated aluminium-adjuvanted influenza vaccines prepared from strains with a pandemic potential as they would be administered to a naïve population (e.g. young children). Such vaccines could direct the cellular immune system of vaccinees towards a predominantly Th2 response, making them more prone to serious influenza disease during subsequent infection. Specific studies in animals should be considered to address this concern (see 4.2.1.1).

- Investigation of local and systemic tolerance of repeated doses administration is also required when the intended vaccination schedule consists of multiple doses of vaccine containing in total considerably more than 45 µg of HA antigen.

- Use of any of the influenza vaccine types mentioned above in combination with a well-established adjuvanting system will also only require local tolerance studies following administration of single and repeated doses.

- Influenza vaccines derived from an entirely new production process will require a complete non-clinical study program as stipulated in the relevant guidelines.

- New adjuvanting systems – in particular when combined with influenza virus antigens from a new or modified manufacturing process - where no experience exists in relation to human use need to be specifically investigated for their safety profile, separately and in combination with the influenza virus antigen. 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, i.e. once before (as a priming) and once during the pregnancy phase (groups with different time points might be considered).

It is expected that non-clinical safety testing should normally be performed with vaccine that contains the strain intended for the candidate vaccine. If some or all of the data have been obtained with seasonal vaccine strains or other strains with the potential to cause a pandemic, the applicant should justify the relevance of these data. If reference is made to the literature as supportive bibliographic data, this literature should be provided and its relevance to the candidate influenza vaccine should be discussed.

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. Clinical requirements*

In principle, the clinical development of influenza vaccines prepared from a virus with a pandemic potential should be in accordance with the general recommendations regarding the clinical development of vaccines. Therefore, the Guideline on Clinical evaluation of New Vaccines (EMEA/CHMP/VEG/164653/05) applies where appropriate.

In the pre-submission phase the applicants are encouraged to present and discuss with European competent authorities the clinical development plan and any interim results.

**Target population**

The SPC for each candidate vaccine will reflect the characteristics (e.g. age range, immune status) of the population(s) in which it is considered that sufficient data are available to support a dose regimen that will be potentially protective.

It is possible that the manufacturer will not be able to generate data for all age and risk categories. Under these circumstances, some degree of extrapolation might be allowed (e.g. from healthy adults to older and younger age categories). The appropriateness and extent of any extrapolation that is allowed will have to be considered on a case-by-case basis and will depend on the data available. Applicants proposing such extrapolations should seek Advice from European competent authorities.

As with all vaccines, variations to the SPC that extend the population in which dose recommendations have been established may be approved if suitable data are provided.

In principle, studies in children and adolescents to evaluate immunogenicity and safety should be initiated only after acceptable data have been obtained from studies conducted in healthy adults.

Studies in infants and toddlers should only be initiated when data from older children and adolescents have been found acceptable.

**Immunological assessment and criteria**

Clinical studies should provide a detailed characterisation of immunological responses to the strain in the candidate influenza vaccine, which should be the strain intended for the final product. Data generated during clinical studies conducted with vaccines manufactured similarly but containing other influenza viruses, including other strains with a potential to cause a pandemic or seasonal influenza strains, may be considered to be supportive.

The comprehensive results from the HI, SRH and microneutralisation assays will form the basis for the assessment of immunogenicity. The choice of methodology and the standardisation of the assays should be addressed by the applicant. Applicants should predefine in the protocol which immunogical parameter(s) will be used in the primary analysis of immunogenicity.

The seroprotection criterion of at least 1:40 for the HI titre that is applied to the assessment of immunogenicity of seasonal influenza vaccines is based upon the assumption of a correlation with a reduction in influenza-like illness when most of the vaccinated population has some degree of pre-existing immunity against the vaccine strains. This criterion may not be valid for vaccines prepared from an influenza virus with the potential to cause a pandemic and to which the population would be immunologically naive. Alternative cut-off points should be discussed and possibly justified.

As generally stipulated for vaccines used for primary immunisation of a previously immunologically naïve population, influenza vaccines used for pandemic preparedness should induce high seroprotection rates, preferably after one or at most two doses. All three criteria (seroprotection rate, GMT increase and response rate) as defined in guideline CPMP/BWP/214/96 should be fulfilled.

A demonstration that the candidate vaccine elicits neutralising antibodies directed against the vaccine strain is very important. The neutralising antibody titre that correlates with seroprotection is, at present, unknown. Neutralising antibody should be measured in at least a subset of vaccinated individuals, preferably at one or a few selected reference centres with the appropriate expertise. The proportions achieving at least a fourfold increase in the antibody titre and the GMTs should be reported along with a reverse cumulative distribution curve.

Although additional immunological assessments, such as explorations of cell-mediated immunity and neuraminidase inhibition, are of unknown relevance to protection, these should be explored in a subset of vaccinees to provide more insight into the overall effects of vaccination.

Antibody kinetics after the first and second dose should be described. Immune responses should also be determined at intervals after completion of the primary series in at least a statistically valid subset of the vaccinated population to investigate the need for revaccination. At the time of initial authorisation, these data may be limited (e.g. to 6-12 months for only a subset of the vaccinated population). It will be expected that applicants will have plans in place and commit to follow antibody levels over time (post approval commitment).

**Dose and schedule**

In order to support the dose and regimen that are proposed in the SPC, studies should evaluate immune responses after single and multiple doses. Anti-HA antibodies should be assessed by means of HI and/or SRH assays. Virus neutralisation should also be assessed after single and multiple doses in at least a subset of vaccinees (see above under immunological assessment and criteria).

The optimal dose and schedule may depend upon:

- Vaccine specific factors, such as type and amount of antigens, content and type of adjuvant;
- Population specific factors such as age, immunological naivety to the strain.

If the data indicate that more than one dose of vaccine is needed to achieve potentially adequate and/or optimal immune responses, consideration should be given to evaluating the minimum dose interval that might be employed.

**- Initial dose finding studies**

In general, for each specified population group naïve individuals (i.e. HI titre < 1:10) should be studied for each dose and/or proposed schedule that is investigated to identify formulations (e.g. dose of antigen and amount of adjuvant, if needed) and schedules that elicit potentially adequate serological responses. The number of subjects studied per dose group should be statistically justified, but be at least 50.

**- Dose confirmatory studies**

Once the applicant considers that an appropriate formulation and schedule has been identified for healthy adults aged from approximately 18-60 years, the safety and immunogenicity of the final choice should be evaluated in larger numbers in a similar population. The total database for safety in this first population to be studied should be as shown in table 1 and discussed below. A substantial proportion (to be justified by the applicant) of the additional subjects vaccinated should also be studied for immunogenicity. If some age groups (e.g. persons of a particular decade between 18-60 years) were underrepresented in the initial dose finding study, particular efforts should be made to obtain further data in the dose confirmatory study.

Extension of the population in which the vaccine may be indicated for use (e.g. by age group and/or risk factors) may be based on studies completed before or after initial authorisation.

**- Induction of immunity to other influenza strains**

As explained above, the primary characterisation of the immune response to a candidate influenza vaccine should focus on assessing the immune responses to the vaccine strain. These data would form the basis for the assessment of immunogenicity before initial authorisation.

However, either before and/or after initial authorisation (see also below) the applicant is expected to investigate or have plans to investigate:

- Cross-reactivity i.e. ability of antibody elicited by the vaccine to react with other viruses in circulation (e.g. cross-reaction of antibody elicited by an H5N1 vaccine to emerging drift variants of H5N1 avian influenza viruses). This should be assessed by means of neutralising antibody tests using different strains in the assay.

- Cross-protection. Information on cross-reactivity as described above may be included in section 5.1 of the SPC. However, no claims for cross-protection can be made unless the cross-reactivity data are supplemented by evidence that vaccinated animals are protected against infection following challenge with other strains.

In addition, applicants are encouraged to investigate the potential for cross-priming i.e. examination of the immune responses of individuals primed with the candidate vaccine to a vaccine containing another strain of virus (see also section 4.3 - Dose and schedule and section 4.4).

**Safety**

The size of the safety database for each influenza vaccine prepared from a virus with a pandemic potential will be different, depending on the population studied, as defined in table 1.

Table 1:

| **Size of the safety database required to detect ADRs occurring at a frequency as stated below*:** | |
|---|---|
| Adults from 18 to 60 years | ≤ one in one thousand persons vaccinated (i.e. rare ADRs)<br><br>(e.g. a database of approximately 3000 subject might be sufficient) |
| *Specified age groups*<br><br>(e.g. infants, children, adolescents, adults over 60 years of age) | ≤ one in one hundred (i.e. uncommon ADRs)<br><br>(e.g. a database of approximately 300 subjects from each specified age group might be sufficient) |
| *Specified risk groups*<br><br>(e.g. immune compromised individuals, chronically ill patients) | ≤ one in one hundred (i.e. uncommon ADRs)<br><br>(e.g. a database of approximately 300 subjects from each specified risk group might be sufficient) |

* Applicants are encouraged to discuss the proposed size of the safety database with competent regulatory authorities during the clinical development programme.

Follow-up for the evaluation of safety should be at least 6 months after the last dose of vaccine. For reactogenicity evaluation, at least all the parameters defined in guideline CPMP/BWP/2490/00 should be studied. These data should be submitted before initial marketing authorisation.

If any new issues regarding safety arise during the clinical development programme, these need to be adequately addressed before authorisation and followed up specifically as part of the risk management plan.

**Post-approval commitments and Risk management plan**

As mentioned above, at the time of initial authorisations 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 (e.g. persons dealing with avian influenza outbreaks in flocks or close contacts of documented cases of human infection due to such viruses) information on breakthrough cases should be collected. 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. Such data would be informative for planning future pre-pandemic vaccination strategies and, 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.

If the strategy in any one 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.

In both the instances described, and depending in part on the number of different pre-pandemic vaccines that may have been distributed in a population, it may or may not be possible to assess vaccine-specific protection as well as the overall effectiveness and safety of the chosen strategy. It is acknowledged that monitoring effectiveness and safety under both scenarios will be fraught with difficulties and will need careful pre-planning, most likely in close conjunction with public health authorities. Any plans in this regard should be provided in the Risk Management Plan (RMP) or be included in updates of the RMP.

### *4.4. Post authorisation issues for influenza vaccines prepared from viruses with pandemic potential*

It is possible that MAHs might wish to propose replacement of the strain in an approved vaccine. For example, this might occur if sequential studies show low or negligible cross-reactivity and cross-protection to drift variants and/or if expert opinion suggests that the HA subtype of influenza virus most likely to trigger a pandemic has changed. Two scenarios could occur and have different regulatory implications as follows:

a. Replacement of the strain in the approved vaccine with a different strain of the same subtype (e.g. supplanting the original H5N1 with another H5N1 strain). In this case the MAH would have to submit all manufacturing and quality data related to the new strain. A clinical study should be conducted to demonstrate that immune responses to the new vaccine strain are adequate (see section 4.3: Immunological assessment and criteria). If feasible it is recommended that the vaccine prepared from the replacement strain should also be administered to a cohort that previously received the original strain vaccine in order to assess cross-priming. Applicants are advised to obtain advice from EU competent authorities regarding the extent and type of clinical data that would be required.

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

## REFERENCES


1) Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation (EMEA/CPMP/VEG/4717/03)

2) Cell Culture Inactivated Influenza Vaccines – Annex to Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/2490/00)

3) Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004)

4) Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95)

5) Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96)

6) Note for Guidance on the Clinical Evaluation of Vaccines (CHMP/VEG/164653/05)

European Medicines Agency
*Evaluation of Medicines for Human Use*

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

# GUIDELINE ON DOSSIER STRUCTURE AND CONTENT FOR PANDEMIC INFLUENZA VACCINE MARKETING AUTHORISATION APPLICATION (Revision)

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## TABLE OF CONTENTS