COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

GUIDELINE ON DOSSIER STRUCTURE AND CONTENT FOR PANDEMIC INFLUENZA VACCINE MARKETING AUTHORISATION APPLICATION

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1. GENERAL INTRODUCTION

1.1. Procedural issues

Pandemic influenza can occur at any time of year and may spread rapidly throughout the world. Vaccines will form the main prophylactic measure against pandemic influenza and will play an important role in national and EU pandemic preparedness plans. Speed in vaccine development is vital and this guideline provides the basis for a fast track licensing procedure for pandemic vaccines within the EU. The procedure involves the submission and approval of a core pandemic dossier during the interpandemic period, followed by a fast track approval of the pandemic vaccine, based on the submission of a pandemic variation1.

Core pandemic dossier

In the core pandemic dossier, the applicant should justify the development strategy, validate production processes and analytical methods, and report the findings from preclinical tests (if relevant) and clinical trials. This information should support a vaccination strategy that is likely to be used for a pandemic vaccine.

To achieve this, a “mock-up” vaccine should be produced, ideally in the same way as the intended pandemic vaccine (cell culture or egg derived, whole virion, split or subunit vaccine), have the same antigen content and same adjuvant system (if used) and use the same route of administration. The antigens in the mock-up vaccine should be different from those in the influenza viruses currently circulating, i.e. ‘novel’ antigens, in order to simulate a situation where the target population for vaccination is immunologically naïve.

Considering the variety of possible pandemic vaccines, it is difficult to provide specific guidance in the core pandemic dossier on what is needed for each vaccine type. Consequently, the guidance will provide some general principles suitable for all types of vaccine and where necessary, some more specific guidance.

Pandemic variation

A pandemic variation application will contain only the quality data that is new and relevant for the pandemic strain. It is expected that pre-approval preclinical and clinical data with the pandemic strain will not be present in the pandemic dossier; Marketing authorisation holders are expected to gather clinical information with the pandemic vaccine as the influenza pandemic progresses.

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

1.2. Legal framework

Directive 2001/83/EC, as amended, lays down in Article 8 the requirements for a marketing authorisation application and Council Regulation (EEC) 2309/93, as amended, 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

1 Where the submission is done via the centralised route, this guideline should be read in conjunction with the Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (EMEA/CPMP/VEG/4986/03).
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 aims to provide guidance to the industry 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.

3. **QUALITY**

As for inter-pandemic influenza vaccines, pandemic influenza vaccines shall be produced in either embryonated hens’ eggs or on a cell substrate. 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 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. **Vaccine reference virus**

**Definition**

A vaccine reference 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 reference virus for vaccine production and to establish a vaccine seed lot.

**Reference virus**

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

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2 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.
a) A reassortant virus containing the haemagglutinin (HA) genome segment of a highly pathogenic virus, 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 and the remaining six 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 reference viruses suitable for use as mock-up vaccine strains:
- 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 reference 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 strains, that are then made available by a WHO Collaborating Centre to vaccine manufacturers. Such viruses are either wild-type influenza viruses or reassortants based on PR8. Where the preparation of the vaccine reference virus involves reverse genetics, there are additional quality considerations beyond those involved with annual vaccine production.
Reverse genetics (options a and possibly b) requires the use of mammalian cells for development of a vaccine reference virus and this imposes additional requirements to assure the safety and quality of the product. In view of the use of mammalian cells for the development of reference strains 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 (see Ph. Eur. general chapter 5.2.3. on cell substrates for the production of vaccines for human use)

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3 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.
- Materials used in generating a reference virus via reverse genetics process must be compliant with the current version of the Transmissible Spongiform Encephalopathy Note for Guidance
- 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 reference virus produced has been assessed by a WHO collaborating laboratory to conclude that antigenic, genetic and phenotypic characteristics make the strain suitable for general use. This includes, when appropriate, testing in animals to demonstrate elimination of high pathogenicity4 (see also in Non-clinical section).
- A protocol is prepared, summarising virus development and documenting the items listed above. An example of such a protocol prepared for an H5N1 vaccine virus development is given in Annex 1.

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 2. Manufacturers should adhere to National or Regional Health and Safety regulations.

3.1.2. 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 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.

3.1.3. 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 CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00).

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 evaluated5, 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.

4 The virus will be tested for non-pathogenicity in chickens and ferrets according to protocols approved by the OIE (www.oie.int) and WHO respectively.
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.

Adjuvants
There is increasing evidence that an adjuvant may be needed in order to illicit a satisfactory immune response in naïve individuals. The quality aspects of the use of adjuvants should be discussed with the European competent authorities.

Stability
Stability data for the mock-up vaccine should be developed as described in Ph. Eur monograph of Vaccines for Human Use (2002:0153). A protocol for testing pandemic vaccine stability should be developed, using data from the mock up vaccine.

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 strains.
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 strain shall be approved by the CPMP.

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.

Testing for extraneous agents
The seed virus for production of the pandemic vaccine shall be shown to fulfil the requirements for 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.

Immunogenicity studies in animals on at least one batch are required in the pandemic variation application. Immunogenicity studies to demonstrate consistency of production should be performed on at least three consecutive batches on an ongoing basis (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 normally.

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

Influenza vaccines have been available for more than five decades and have evolved from crude, whole virus preparations to highly purified split or subunit vaccines, which are the only ones used in the EU nowadays. During influenza vaccine development a considerable amount of knowledge was accumulated on quality, safety and efficacy aspects.

From the safety point of view it is clear that three essential factors, purity of the vaccine preparation, the nature of the antigen (whole virus versus split or subunit vaccine) and amount of antigen, determine the reactogenicity profile of influenza vaccines. Influenza vaccines today are highly purified and very well tolerated although the amount of antigen (about 45 µg of hemagglutinin (HA), 15 µg of HA antigen derived from each recommended strain in a trivalent influenza vaccine formulation) is the highest amongst currently licensed vaccines.

It is important to note that the long clinical experience on the immunogenicity and safety of existing influenza vaccines is an essential part of the benefit-risk analysis. In the developmental process of pandemic influenza vaccines, past and present experiences regarding immunogenicity, safety and tolerability of influenza vaccines can be transferred cautiously to pandemic influenza vaccines. As outlined below, for established influenza vaccine manufacturing procedures, applied to the production of a pandemic influenza vaccine, a reduced non-clinical safety testing program can be considered.

Non-clinical data need to be submitted only in the core pandemic dossier for a “mock up” vaccine. For the pandemic variation in general, the only new non-clinical data which need to be submitted are immunogenicity data (see 4.3)

4.2. Core pandemic dossier

4.2.1 Non-clinical immunogenicity

Immunogenicity data derived from a small animal species that responds properly to human influenza vaccine (e.g. chicken, mice, ferrets etc…) are normally expected before entering into human clinical trials. These investigations include dose finding studies as well as studies on the effect of one or more additional doses given in defined intervals after the first dose. Immunogenicity studies in animals are also useful to document consistency of production, in particular during the validation phase of a pandemic vaccine manufacturing process. These immunogenicity results will be used as a reference for the quality control made on the actual pandemic vaccine.

4.2.2. Non-clinical safety
- For pandemic split or subunit influenza vaccines derived from a licensed manufacturing process similar to inter-pandemic vaccines (apart from the strain), no further non-clinical investigation is required.
- Changes relating to the dosage of split or subunit pandemic vaccines derived from a licensed process will also not require non-clinical safety testing unless a single human dose exceeds 45 µg of HA antigen. In the latter case a study on local tolerance of single and repeated dose administration is required.
- Investigation of local tolerance of repeated doses administration is also required when the intended vaccination schedule consists of multiple doses of vaccine containing in total more than 45 µg of HA antigen, to achieve an acceptable immune response.
- The same principles as described in the previous two bullet points apply for pandemic influenza vaccines based on whole virions derived from a licensed manufacturing process.
- Use of any of the pandemic 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.
- The core pandemic dossier for pandemic influenza vaccines derived from an entirely new production process will require a complete non-clinical study program as stipulated in the relevant guidelines. If relevant, data from the developmental phase using interpandemic vaccine strains are acceptable. If reference is made to the literature as supportive bibliographic data, this literature should be provided and its relevance to the pandemic influenza vaccine concept should be discussed in the core pandemic dossier. The lack of specific non-clinical studies should be justified.
- New adjuvanting systems 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.

For reduction of or exemption from a non-clinical safety investigation program for a mock-up vaccine in the core pandemic dossier, European competent authorities should be consulted for Scientific Advice.

4.2.3. Challenge experiments
Additional studies in animals to provide further evidence on the efficacy of a pandemic vaccine, such as challenge studies in mice, ferrets or other animals, should also be conducted if possible (see section 3.1.1). However, challenge studies using either an attenuated pandemic strain or even a non-genetically manipulated potentially highly virulent original pandemic influenza virus strain, can only be performed in appropriate, dedicated facilities (see also Annex 2).

4.3. Pandemic variation
The only new non-clinical data that need to be submitted are immunogenicity data for the first three batches to document consistency of production.

If an attenuated pandemic influenza virus strain obtained through an official WHO influenza collaborating centre is further genetically manipulated for reasons to be justified, maintenance of attenuation must be demonstrated by a suitable test in animals, for example the chicken intravenous pathogenicity test, or a pathogenicity test performed with ferrets.
5. CLINICAL REQUIREMENTS

5.1. General considerations for the clinical development programme

The proposals for the provision of clinical data that are made in this section are based on the assumption that the approval of a pandemic influenza vaccine will be in two stages as stated in section 1 of this Guideline.

Firstly, the clinical efficacy and safety data that should be included for the approval of a mock-up vaccine in the core pandemic dossier are considered. The development of the mock-up vaccine is based on a proof of concept principle. The clinical data are obtained during the inter-pandemic phase with a vaccine that includes viral antigen(s) to which humans are immunologically naïve.

Secondly, unless the mock-up vaccine is suitable for vaccination during a subsequent pandemic, it is necessary to consider the additional clinical data that should be submitted for an actual pandemic vaccine. If the final pandemic vaccine is of a similar nature and is produced in the same way as the mock-up vaccine that was the subject of the core pandemic dossier it would acceptable to extrapolate the clinical data from the core pandemic dossier to the final pandemic vaccine.

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 known whether the immunological criteria that are currently applied to the clinical data supplied for the annual strain variation procedures for existing inactivated influenza vaccines are relevant to the assessment of potential pandemic vaccines. Therefore efforts should be made to obtain additional information on clinically relevant correlates of protection. Prior to initiating and during a clinical trial program the MAH should consider the current and novel reports in the literature on the immunology, efficacy and safety of inactivated influenza vaccines. In particular, any relevant data on the relationship between the immune response to vaccination and clinical efficacy should be taken into account in the design, interpretation and discussion of the immunological studies that are generated with the mock-up vaccine (see 5.2.3). In advance of an actual pandemic, protocols should be in place that plan for investigation of immunological responses to the pandemic vaccine (particularly in children, see 5.2.1) and of the relationship between immunological responses to vaccination and clinical protection during an actual pandemic (see 5.3.4).

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 “Note for Guidance on the Clinical Evaluation of New Vaccines (CPMP/EWP/463/97)” have to be fulfilled depends upon several factors. These include the extent to which the strains for the mock-up influenza vaccine are shown, in pre-clinical studies, to be similar to conventional inactivated influenza vaccine strains.
5.2. The Core pandemic dossier and the mock up vaccine

Clinical trials on protective efficacy for the mock-up vaccine cannot be performed. Therefore, studies that provide a detailed characterisation of the immunological responses to the mock-up vaccine are required.

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

5.2.1 Target population

For the purpose of the core pandemic dossier clinical data may be obtained solely from healthy adults of various age groups.

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 initial core pandemic dossier, it is recommended that at least limited data on safety should be obtained from healthy children. These data 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 pandemic vaccine in children.

5.2.2 Design of clinical trials

The clinical development program should be based upon trials that directly compare different dose levels of antigen and/or adjuvant and/or various immunisation schedules.

In the absence of protective efficacy trials, the total number of subjects exposed in clinical trials for the core pandemic dossier will likely not be very large. However, the numbers of subjects within each trial should be adequate to ensure that the data are statistically valid (see CPMP/EWP/463/97). Sample sizes that are acceptable for the assessment of immune responses in annual updates (CPMP/BWP/214/96) are considered to be insufficient to describe the immunogenicity of the mock up vaccine. Wherever possible, 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.

5.2.3 Immunological assessment criteria

The criterion of an HI titre of at least 40 IU 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 inter-pandemic strains. This may not be valid for pandemic influenza vaccines. In a pandemic situation older people may retain some immunity and mortality rates may, at least initially, be higher in younger adults. 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 or older adults in CPMP/BWP/214/96. In addition, neutralising antibodies should be measured, preferably at one or a few selected reference centres.

During the course of the clinical development programmes, the data that are accumulated with the various mock up vaccines or from other ongoing research may indicate that 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 CPMP. Therefore, companies that are developing mock up vaccines should consult with European competent authorities at intervals as may be felt appropriate during the development process.

To assess the possible need for revaccination to cover (a) subsequent wave(s) of the pandemic, immune responses should be determined after 6 and 12 months have elapsed since completion of the primary series in at least a statistically valid subset of the vaccinated population.

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.

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, several potentially feasible vaccination schedules should be explored. The optimal dose and schedule 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 least all the parameters defined in CPMP/BWP/2490/99.

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 necessarily contain thiomersal. In accordance with CPMP guidance, the level should be kept to the minimum necessary. The applicant should discuss the final thiomersal content of the vaccine. In addition, if an adjuvant(s) is to be used, any specific safety questions that may arise from the preclinical database should be investigated in the clinical trials.
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, MAHs 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.

The principles and definitions laid down in the "Protocol for the evaluation of the quality and clinical data within the European surveillance scheme" may be used. Additionally, MAHs may seek scientific advice from European competent authorities. The MAHs should collaborate with European health authorities in order to assure adequate performance of post-marketing surveillance.

5.3. The Pandemic variation and the Final pandemic Vaccine

5.3.1 Initial approval for use

In the case of an actual pandemic, the vaccination programme would need to be implemented as soon as possible. Provided that the mock-up and final pandemic vaccines are similar other than in strain content 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.

5.3.2 Post-approval clinical investigations

See also 5.2.6 above regarding post-approval commitments for mock-up vaccines. The emergency use of a product is not an ideal situation for the conduct of an organised programme of post-marketing evaluations. However, it will be very important to obtain safety, immunogenicity and effectiveness data for the final pandemic vaccines if the situation arises.

The accumulation of immunogenicity, effectiveness and safety data should be a co-operative effort between companies and national and international public health authorities. Facilities for the rapid sharing of these data should 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.

5.3.3 Immunogenicity

As soon as there are sufficient stocks of the final pandemic vaccines available, each applicant 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. Should the mock up vaccine be suitable for use in a pandemic, and then the clinical data that was provided in the core dossier should be supplemented according to the extent of the information that was provided before approval.

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6 Aguilera JF. "Protocol for the evaluation of the quality and clinical data within the European surveillance scheme. EISS Protocol, December 2002."
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.

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

5.3.5 Safety
Unless the mock up vaccines are also suitable for use as final pandemic vaccines, all the safety data on the final pandemic vaccines will have to come from real life use. However, even if mock-up vaccines are suitable, the post-marketing safety data will be extremely important, since the core pandemic dossier will be too limited in size for full assessment of safety. 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 during a pandemic should follow as far as possible the pharmacovigilance requirements as laid down in Note for Guidance (CPMP/ICH/377/95).
6. REFERENCES

- 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)
- Influenza vaccine (split virion, inactivated); Ph. Eur. 01/2002:0158
- Influenza vaccine (surface antigen, inactivated); Ph. Eur. 01/2002:0869
- Influenza vaccine (surface antigen, inactivated, virosome); Ph. Eur. 01/2004:2053
- Influenza vaccine (whole virion, inactivated); Ph. Eur. 01/2002:0159
- Vaccines for human use, Ph. Eur. 07/2002:0153
- Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95)
- CPMP Note for Guidance on the Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
ANNEX 1
INFLUENZA VIRUS PRODUCED BY REVERSE GENETICS DERIVATION FROM A HIGHLY PATHOGENIC PRECURSOR (EXAMPLE)

Virus description: a reverse genetics derived 2:6 reassortant between A/abc/123/04 and A/PR/8/34
Passage history: Vero x, Egg x

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SOP/Method</th>
<th>Results/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/abc/123/03 virus growth in eggs</td>
<td>SOP xyz, at BSL4 containment</td>
<td>Original egg grown virus from ...</td>
</tr>
<tr>
<td>Cloning and genetic modification of A/abc/123/04 HA segment</td>
<td>Standard molecular biological techniques</td>
<td>A/abc/123/04 HA segment cloned with polybasic cleavage site excised and stabilising mutations introduced</td>
</tr>
<tr>
<td>Sequencing of cloned HA</td>
<td>Plasmid DNA cycle sequencing</td>
<td>A/abc/123/04-like with absence of polybasic amino acids at cleavage site</td>
</tr>
<tr>
<td>Cloning of A/abc/123/04 NA segment</td>
<td>Standard molecular biological techniques</td>
<td>A/abc/123/04 NA segment cloned unmodified</td>
</tr>
<tr>
<td>Sequencing of cloned NA</td>
<td>Plasmid DNA cycle sequencing</td>
<td>A/abc/123/04-like</td>
</tr>
<tr>
<td>PR8 plasmids</td>
<td>Standard molecular biological techniques</td>
<td>Prepared by ... or Provided by ...</td>
</tr>
<tr>
<td>Plasmid preparation</td>
<td>SOP xyz</td>
<td>Plasmids HAxx and NAzz used plus six PR8 ‘backbone’ and four helper plasmids</td>
</tr>
<tr>
<td>Vero cells</td>
<td>SOP xyz</td>
<td>Cells are validated for human vaccine manufacture</td>
</tr>
<tr>
<td>Reverse genetics</td>
<td>SOP xyz</td>
<td>The Vero cell rescued virus was passaged twice in eggs; HA titre abc</td>
</tr>
</tbody>
</table>
Influenza Virus Produced by Reverse Genetics
Finished Product Specification (Example)

Virus description: a reverse genetics derived 2:6 reassortant between A/abc/123/04 and A/PR/8/34

Passage history: Vero x, Egg x

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SOP/Method</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigenic analysis of virus</td>
<td>SOP xyz</td>
<td>A/abc/123/04-like</td>
<td>Complies with specification</td>
</tr>
<tr>
<td>Virus titre</td>
<td>SOP xyz</td>
<td>N/A</td>
<td>HA titre of ...</td>
</tr>
<tr>
<td>Infectivity in eggs</td>
<td>SOP xyz</td>
<td>N/A</td>
<td>10^3 EID&lt;sub&gt;50&lt;/sub&gt;/ml</td>
</tr>
<tr>
<td>HA sequence of virus</td>
<td>RT-PCR/cycle</td>
<td>A/abc/123/04-like with absence of polybasic amino acids at cleavage site</td>
<td>Complies with specification</td>
</tr>
<tr>
<td>NA sequence of virus</td>
<td>RT-PCR/cycle</td>
<td>A/abc/123/04-like</td>
<td>Complies with specification</td>
</tr>
<tr>
<td>Chicken pathogenicity test</td>
<td>SOP xyz</td>
<td>IVPI 1.2 or less</td>
<td>Result ...</td>
</tr>
<tr>
<td>Ferret pathogenicity test</td>
<td>SOP xyz</td>
<td>Viral titres in respiratory tissue no greater than parental viruses. Virus replication restricted to respiratory tract. Clinical symptoms indicative of attenuation.</td>
<td>Complies with specification</td>
</tr>
<tr>
<td>Egg embryo test</td>
<td>SOP xyz</td>
<td>Does not kill embryos</td>
<td>Complies with specification</td>
</tr>
<tr>
<td>Sterility</td>
<td>SOP xyz</td>
<td>Meets requirement</td>
<td>Complies with specification</td>
</tr>
<tr>
<td>Contamination of virus with plasmid DNA</td>
<td>PCR</td>
<td>N/A</td>
<td>Result ...</td>
</tr>
<tr>
<td>Animal materials used during derivation of virus</td>
<td>Traceability of materials</td>
<td>Compliance with EU Guideline on TSE</td>
<td>Complies with specification</td>
</tr>
</tbody>
</table>

N/A: not applicable
ANNEX 2

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.