



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

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**GUIDELINE ON DOSSIER STRUCTURE AND CONTENT OF MARKETING
AUTHORISATION APPLICATIONS FOR INFLUENZA VACCINES DERIVED FROM
STRAINS WITH A PANDEMIC POTENTIAL FOR USE OUTSIDE OF THE CORE
DOSSIER CONTEXT**

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GUIDELINE ON DOSSIER STRUCTURE AND CONTENT OF MARKETING AUTHORISATION APPLICATIONS FOR INFLUENZA VACCINES WITH AVIAN STRAINS WITH A PANDEMIC POTENTIAL FOR USE OUTSIDE OF THE CORE DOSSIER CONTEXT
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EXECUTIVE SUMMARY

This guideline addresses the quality, non-clinical and clinical dossier requirements for influenza vaccines containing or derived from avian strains with a pandemic potential that are intended for use in humans 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.

1. INTRODUCTION

The *Note for Guidance on dossier structure and content for pandemic 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 containing or derived from avian strains with a pandemic potential (such as H5N1 avian influenza strains) outside of the context of a core dossier (see Annex for such possible uses).

2. SCOPE

This guideline is intended for applicants preparing marketing authorisation applications for influenza vaccines containing or derived from avian strains with a pandemic potential that are intended for human use outside of the context of a core dossier.

The guideline addresses the content of marketing authorisation applications for inactivated avian influenza vaccines produced in eggs or in cell cultures. The recommendations in this Guideline are also valid for vaccines containing or derived from influenza strains with a high pandemic potential from other animal (e.g. porcine) or of non-H1/H3 human origin.

This guideline does not address the requirement for development and authorisation of live attenuated avian influenza vaccines.

Applications for avian influenza vaccines for human use are submitted and evaluated during the inter-pandemic or pandemic alert period and will follow the normal procedures for the authorisation of new vaccines. The indication for use in these marketing authorisations (i.e. encompassing use before a pandemic is declared) will distinguish these marketing authorisations from those for seasonal influenza vaccines or for mock-up vaccines (i.e. during a declared pandemic).

It is important to note that the granting of marketing authorisations for avian influenza vaccines for human use should not be interpreted as any sort of endorsement of, or recommendation for, the use of such a vaccine in the pandemic alert period (WHO phase 3 onwards; see Annex). Any decisions to recommend the use of avian influenza vaccines for human use 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, the data presented in a dossier for avian influenza vaccines for human use shall all be derived from a vaccine prepared with the strain against which protection is claimed. Any data with other strains that may or may not belong to the same clade, could be considered to be supportive.

There is increasing evidence that an adjuvant may be needed in order to elicit a satisfactory immune response in naïve individuals. Applicants should consult the Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004).

4.1. *Quality requirements for avian influenza vaccines for human use*

Vaccine reference virus

The vaccine reference virus shall be derived from a circulating avian, porcine or non-H1/H3 human strain with pandemic potential using one of the techniques described in section 3.1.1 of the *Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation* (CHMP/VEG/4717/03).

Alternatively, manufacturers might develop vaccines on the basis of library strains or seeds of avian or other animal or non-H1/H3 human influenza strains, provided that a high degree of antigenic cross-reactivity with circulating avian strains has been shown. The choice of strain should be justified by the applicant. 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 Ph.Eur. monographs for inactivated influenza vaccines¹ 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

¹ See following Ph. Eur. monographs on inactivated influenza vaccines: 2006:0158 ; 2006:0159 ; 2006:0869 ; 2006: 2053; 2006:2149 ; 2006:2308.

inactivated influenza vaccines produced in cell cultures and 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, an effective antimicrobial preservative should be evaluated², 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.

- 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 avian influenza vaccine should be developed as described in Ph. Eur monograph of Vaccines for Human Use (2006:0153). 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.

Depending on the anticipated use, the vaccine might be stored for a longer timeframe than seasonal influenza vaccines ("stockpiling"). Applicants should take this into account in the stability protocols. Periodic non-clinical and/or clinical reinvestigation of a stockpiled vaccine might become necessary. The final stability testing program should be agreed on by a competent authority.

4.2. *Non-clinical safety and immunological requirements for avian influenza vaccines for human use*

Non-clinical immunogenicity

Immunogenicity data derived from a small animal species that responds well to human influenza vaccine (e.g. chicken, mice, ferrets) are expected before commencing 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. These studies should also address the need and role of the adjuvant, if included.

Immunogenicity studies in animals are also useful to document consistency of production, in particular during the validation phase of an avian influenza vaccine manufacturing process. Immunogenicity data for the first three batches should be included in the application to document consistency of production.

² See Ph. Eur. General chapter 5.1.3. Efficacy of antimicrobial preservation and Monograph 2006:0153 on Vaccines for human use.

Non-clinical safety

- For split or subunit avian influenza vaccines for human use manufactured and formulated similar to the licensed inter-pandemic vaccine (apart from the strain) or similar to the licensed mock-up vaccine, non-clinical safety investigations 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.
- Changes relating to the dosage of split or subunit avian influenza 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.
- The same principles as described in the previous two bullet points apply for avian influenza vaccines based on whole virions derived from a licensed manufacturing process.
- Use of any of the avian 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.
- Avian 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.

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

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

Non-clinical efficacy

For avian influenza vaccines for human use, protective efficacy cannot be established in clinical trials. Therefore, challenge studies (e.g. in mice, ferrets or other relevant animals) to provide evidence regarding the potential protective efficacy of an avian influenza vaccine in man should usually be conducted using the vaccine that contains the strain intended for the final product. If the applicant submits data from challenge studies performed with mock-up pandemic strains or other avian influenza strains the relevance of the findings to the final product should be justified.

4.2. Clinical requirements for avian influenza vaccines for human use

In principle, the clinical development of avian influenza vaccines for human use should be in accordance with the general recommendations regarding the clinical development of vaccines. The Note for Guidance on Clinical evaluation of Vaccines (EMEA/CHMP/VEG/164653/05, released for consultation in May 2005) 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 avian influenza vaccine for human use will strictly reflect the characteristics (e.g. age range and/or 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.

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.

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 total data available. Applicants seeking such extrapolations should seek Advice from European competent authorities.

Once the EU Paediatric Regulation has come into operation, a Paediatric Investigation Plan (PIP) will need to be submitted as part of the application. Applicants should consult the EMEA website for more information on the procedure for submission and the content of PIPs.

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 avian influenza vaccine that contains the strain intended for the final product. Data generated during clinical studies conducted with other avian influenza strains, mock-up strains or seasonal influenza strains may be considered to be supportive.

The conventional seroconversion criterion of at least 40 IU for the HI titre 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 correlation may not be valid for avian influenza vaccines.

As generally stipulated for vaccines used for primary immunisation of a previously immunologically naïve population, influenza vaccines used for pandemic preparedness should induce high GMTs and seroconversion rates, most preferably after only two doses. More specifically, all three criteria (seroconversion rate, seroconversion factor and significant increase in GMT) as defined in guideline CPMP/BWP/214/96 should be exceeded, with seroconversion rates being the most important.

In addition, neutralising antibodies should be measured in at least a subset of vaccinated individuals, preferably at one or a few selected reference centres. 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.

Immune responses should 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 licensure, these data may be limited (e.g. to 6-12 months and for only a subset of the vaccinated population). It will be expected that applicants will have plans in place to follow antibody levels over time and commitments to this effect will be agreed at the time of first approval.

Also, as part of post-approval commitments, the applicant should investigate cross-reactivity elicited by the vaccine to circulating avian influenza viruses (i.e. drift variants). Emerging information can be included in section 5.1 of the SPC. However, no clinical claims of cross-protection against drift variants can be made without provision of additional evidence (e.g. protection demonstrated in challenge models).

Dose and schedule

Considering the naivety of the population and the use of an inactivated vaccine, a single dose primary regimen is unlikely to be sufficient to elicitate a satisfactory immune response. 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, content and type of adjuvant
- Population specific factors such as age, immunological naivety to the avian strain(s)
- The circumstances of use. For example, a short duration regimen would be needed to urgently achieve seroprotection of persons who might come in contact with the virus, such as poultry workers.

In general, for each specified population group at least 50 immunologically naïve individuals should be studied for each dose and/or regimen that is investigated to identify formulations (e.g. dose of antigen and amount of adjuvant, if needed) and schedules that elicit acceptable serological responses (see table 1).

Table 1: Dose finding and safety studies by population group

Minimum sample size of immunologically naïve individuals to be studied at each dose and /or regimen in studies performed to identify acceptable formulations and schedules	Size of safety database (Based on ADR detection limit)
<i>Adults from 18 to 60 years</i>	
At least 50.	$\leq 0.1\%$
<i>Specified age groups</i> (e.g. infants, children, adolescents, adults over 60 years of age)	
For each specified age group and for each dose and/or regimen investigated, at least 50 immunologically naïve individuals need to be included.	$0.1 - 1\% ^3$
<i>Specified risk groups</i> (e.g. immune compromised individuals, chronically ill patients)	
For each specified risk group and for each dose and/or regimen investigated, at least 50 immunologically naïve individuals need to be included.	$\leq 1\% ^4$

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 the table and discussed below. A proportion of the additional numbers vaccinated (to be justified by the applicant) should also be studied for immunogenicity. Depending on the population included in dose-finding studies, sub-stratification by age may be appropriate to obtain more information in under-represented strata. These strata should preferably be predefined.

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 licensure. The data requirements are summarised in the table.

Safety

The size of the safety database for each avian influenza vaccine will be different depending on the population studied, as defined in table 1.

Follow-up for the evaluation of safety should be at least 6 months and should include at least all the parameters defined in guideline CPMP/BWP/2490/00. These data should be submitted as part of the marketing authorisation application.

³ The size of the safety database depends on the individual clinical investigation programs. Advice from Authorities should be sought.

⁴ For each specific risk group, unless justified.

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

If the avian 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.

Post-approval commitments and Risk management plan

As mentioned above, at the time of initial authorisations plans should be in place to assess antibody persistence, cross-reactivity to new circulating strains and responses to booster doses in cohorts of vaccinees from each age and risk group for which an indication has been granted. There should also be plans ready in case of exposure of any vaccinees to circulating avian influenza strains so that breakthrough cases can be identified and studied. These plans are important to provide insight as to whether prior vaccination may afford at least some protection against strains that might trigger a pandemic.

Whenever the opportunity arises, such as during any government-directed use of vaccine within individual countries, further information should be collected from observational studies to expand the safety and the immunogenicity database. 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, attempts should be made to estimate the effectiveness of prior vaccination in persons who do and do not receive a dose of any pandemic vaccine.

The Risk Management Plan has to provide safety information for each major population group that have not been studied or have only been studied to a limited degree in the pre-authorisation phase.

4.3. *Post authorisation issues for avian influenza vaccines for human use*

As for seasonal influenza vaccines, it might be necessary to change the influenza strain included in the avian influenza vaccine, especially if antibodies raised against the vaccine strain show no or negligible cross reactivity against circulating viruses.

In order to incorporate a new strain (e.g. to supplant H5N1 of clade x with H5N1 of clade y) into the avian influenza vaccine, the marketing authorisation holder will 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 strain in the vaccine are at least as good as were those to the initial strain in the licensed product. Applicants are advised to obtain advice from EU competent authorities regarding the extent and type of clinical data that would be required.

Different requirements would likely apply if there was intent to change the H/N type of strain (e.g. supplant an H7N7 strain into an H5N1 vaccine). Advice from EU competent authorities should be sought on the regulatory framework and data requirements for such a change.

DEFINITIONS

‘Avian influenza vaccines for human use’ and ‘Avian influenza vaccines’ shall mean influenza vaccines with avian strains with a pandemic potential (such as the currently circulating H5N1 avian influenza strains) intended to be used outside of the context of core dossier/mock-up pandemic vaccines as described in the Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation (CPMP/VEG/4717/03).

‘Pandemic influenza vaccines’ are vaccines including the exact matching pandemic influenza strain, for use during the actual influenza pandemic (WHO Phase 6).

REFERENCES

- 1) Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation (EMA/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 vaccine (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, release for consultation May 2005)

Annex: Potential scenarios of use of avian influenza vaccines for human use

Possible scenarios of use of avian influenza vaccines for human use in the Pandemic alert period (Phase 3 onwards) are:

- Use in WHO Phase 3 for pandemic preparedness based on national decisions to recommend vaccination of at least some of the population before there is any evidence of transmission of a potential pandemic strain between humans. The degree of protection that might be conferred by prior vaccination with such vaccines in an actual pandemic situation cannot be predicted since the cross-antigenicity between strains in avian influenza vaccines and the pandemic strain will be unknown.
- Use in WHO Phase 3 and/or later phases (4-5) for protection of those at high risk of exposure to avian influenza (e.g. poultry workers involved in culling exercises, veterinarians and laboratory workers collecting and processing specimens).
- Use in WHO Phases 4 and 5 for pandemic preparedness (e.g. if the vaccine strain was considered a close-enough match to a virus that had been shown to have increased or significant transmission between humans).