



22 September 2011
EMA/CHMP/VWP/734330/2011
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of guidelines for influenza vaccines

Agreed by Vaccine Working Party	September 2011
Agreed by Biologics Working Party	September 2011
Adoption by CHMP for release for consultation	22 September 2011
End of consultation (deadline for comments)	31 December 2011

The proposed guideline will replace guideline / NfG Reference.

- Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure (EMA/CPMP/4986/03)
- Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application (EMA/CPMP/VEG/4717/03 rev. 1)
- Guideline on Influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context (CHMP/VWP/263499/06)
- 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/214/96

Comments should be provided using this [template](#). The completed comments form should be sent to influenzaguideline@ema.europa.eu

Keywords	<i>Influenza guideline, pandemic, seasonal vaccine, pre-pandemic, trivalent inactivated, serological evaluation, protective efficacy, potency assays</i>
----------	--

1. Introduction

Regulatory requirements for the quality, non-clinical and clinical development of influenza vaccines are currently stated in several documents including multidisciplinary guidelines such as EMEA/CPMP/4986/03, CHMP/VWP/263499/06, the *Note for guidance on harmonisation of requirements for influenza vaccines* CPMP/BWP/214/96 and the *Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application* (EMEA/CPMP/VEG/4717/03 rev. 1). These guidelines were drafted and adopted at different time points and over several years before the onset of the 2009-2010 influenza pandemic and each addresses one of seasonal influenza vaccines, pre-pandemic or pandemic vaccines.

The need to update the available guidelines regarding the manufacturing, non-clinical and clinical development of influenza vaccines was recognised during and following the 2009-2010 influenza pandemic. More recently, issues encountered and experience gained during requests for CHMP scientific advice and the processing of several applications for marketing authorisation of influenza vaccines have underlined the desirability of updating the existing guidelines. In addition, it is anticipated that novel influenza vaccines could be based on e.g. recombinant proteins, virus-like particles (VLPs), DNA or live viral vectors and there is a need to consider the regulatory expectations that would apply to such products.

Although current and future influenza vaccines may vary in nature and composition they all aim to prevent clinically manifest influenza by means of eliciting a protective immune response. Therefore the development of a single consolidated guidance document on the quality, non-clinical and clinical requirements for influenza vaccines seems to be both feasible and appropriate.

2. Problem statement

Inactivated trivalent seasonal influenza vaccines (TIVs) have been in use for more than half a century. Nevertheless, several aspects of their use appear to be based on long-established practises rather than on rigorous scientific appraisal. In addition, the assessment of the immunogenicity of these vaccines has been based mainly on two tests (Haemagglutination Inhibition [HI] and Serial Radial Haemolysis [SRH]) that are not standardised and are subject to very considerable inter-laboratory variability. Although correlations between post-vaccination antibody titres assessed by HI or SRH and protection against influenza illness have been described in some age groups they may not be the most reliable or informative measure of immune response when it comes to anticipating efficacy in all sub-populations. For example, the determination of serum neutralising antibody (SNA) titres could potentially be more informative in some population subsets (e.g. influenza-naïve children) but there are relatively few SNA data available for the currently marketed TIVs as well as for monovalent pandemic vaccines.

These and other issues pose problems when attempting to fully understand the possible effects of factors such as lack or presence of detectable antibody prior to first and subsequent doses and the elicitation of immune memory in different age groups on vaccine efficacy. Thus, despite their long usage, there are several unanswered questions regarding the optimal composition and use of inactivated seasonal TIVs in healthy subjects of different ages and in subjects at risk of developing severe influenza and complications of acute infection.

Such uncertainties not only raise problems during the assessment of new inactivated TIVs but also hamper to some extent the assessment of other types of seasonal vaccines (e.g. including those that incorporate an adjuvant or live attenuated viruses) and will have important implications for the evaluation of anticipated novel vaccines. In addition, the issues regarding serological testing raise

questions regarding the type and extent of data that could or should be provided to support annual updates in the antigen content of all types of influenza vaccines.

Many of these same issues arose during the assessment of the pre- and post-approval data that were generated with pandemic and pre-pandemic vaccines. Since pandemics occur when a sufficient proportion of the population is immunologically naïve to allow for sustained viral transmission there were particular concerns regarding the ability of the serological data to support dose regimen selection in different population sub-groups. Additional difficulties arose from issues such as the variability in pre-vaccination antibody as measured using different tests and in many laboratories, the lack of data in some population subsets that might have greatly assisted in recommending regimens during the early days of the 2009-2010 pandemic and the uncertain predictive value of data obtained in non-clinical models. Uncertainties in the assessment of antigen content in batches of vaccine due to variability of the currently used assay – the single radial immunodiffusion assay – and the difficulties in its standardisation have also surfaced for both TIV and pandemic vaccines.

3. Discussion (on the problem statement)

Taking into account all of the above, there appears to be a need to pull together all the available evidence and to re-consider the minimum quality, non-clinical and clinical data requirements to support initial approval of all types of influenza vaccines. It seems essential that this exercise should include a re-appraisal of the serological testing methods and their standardisation. Further thoughts needs to be given to the evidence required to support annual changes in the antigen composition of seasonal vaccines. Possible alternative analytical test(s) to determine the antigen content and composition as well as evaluation of vaccines developed in advance of an actual pandemic situation require special consideration.

4. Recommendation

Taking into account the factors listed in the Problem Statement above, it is recommended that the CHMP should envisage a new set of influenza vaccine guidelines that takes into account all relevant aspects of influenza vaccine science and technology.

Particular issues to be addressed in the new influenza vaccine-specific guideline would include (but are not limited to):

For seasonal, pre-pandemic and pandemic vaccines:

- Further guidance regarding expectations for the serological evaluation of immunogenicity. For example, exploration of pre-vaccination serostatus and its effects on post-vaccination responses, persistence of the immune response (humoral and/or cellular) to vaccine virus and drifted variants and the administration of booster doses using homologous and heterologous virus antigens
- Consideration of the selection of antibody assays and evaluation of their performance. In particular, to address the standardisation of functional assays such as HI, SRH and SNA. Also, to consider the possible role of novel functional assays (e.g. determination of antibody against neuraminidase)
- Consideration of how to improve on the current understanding of the predictive value of the immunogenicity data for vaccine efficacy taking into account the type of vaccine under study
- Specific guidance regarding the evaluation of immune responses in population sub-groups, such as children of different age ranges and immunosuppressed subjects
- Expectations for estimating vaccine efficacy in specific circumstances and populations

- Expectations for estimating vaccine effectiveness in different circumstances of use and especially during pandemic situations
- Consideration of the role of non-clinical models and the most appropriate types of studies to provide an assessment of the immunogenicity and likely protective efficacy of a vaccine construct
- Consideration of how to accumulate non-clinical and clinical data to inform regarding use of a vaccine during pregnancy
- Improvements in the guidance regarding the vaccine quality aspects are needed and would be addressed in the form of specific modules (e.g. seasonal vs. pandemic vaccines). Particular attention will be paid to establishing the timely availability of reliable potency assays and potential alternative assays for antigen determination especially in the frame of strain changes.

For pandemic vaccines:

- The development of 'mock-up' pandemic vaccines, including strain selection and the range of data that would optimally be generated in advance of a declared pandemic situation
- The need for additional studies initiated after the pandemic period or performed as extensions to existing studies in view of emergence of potential drifted variants

5. Proposed timetable

- Adoption of Concept Paper in September 2011 followed by 3 months consultation phase
- Interaction with stakeholders (EVM) in November 2011.
- First draft Guideline in Q1-Q2 2012

6. Resource requirements for preparation

Development of the guideline will be led by the VWP in collaboration with the BWP. A coordinating team will be appointed with representation from the above working parties and the Paediatric Committee (PDCO). Other relevant working parties (e.g. PhVWP) and external stakeholders will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. The VWP and BWP will discuss draft versions at their regular meetings.

7. Impact assessment (anticipated)

The guideline will give applicants and Regulatory Authorities guidance on the assessment of all procedures pertaining to influenza vaccines. Such a harmonized approach will contribute to the development of better characterized influenza vaccines within the EU. It will also streamline the non-clinical and clinical development of novel influenza vaccines.

8. Interested parties

Internal/External parties

EMA: VWP, BWP, PhVWP, PDCO

EDQM and OMCLs

External consultation: pharmaceutical industry, academic networks and learned societies within the EU.

9. References to literature, guidelines, etc.

- Pandemic report and lessons learned - Outcome of the European Medicines Agency's activities during the 2009 (H1N1) flu pandemic, 29 April 2011 (EMA/221017/2011)
(http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/04/WC500105820.pdf)
- Council conclusions on Lessons learned from the A/H1N1 pandemic – Health security in the European Union 3032nd GENERAL AFFAIRS Council meeting Brussels, 13 September 2010
(http://ec.europa.eu/health/preparedness_response/docs/council_lessonsh1n1_en.pdf)