25 July 2013
EMA/CHMP/VWP/232674/2013
Committee for Medicinal Products for Human Use (CHMP)

Explanatory note on the withdrawal of the note for guidance on harmonisation of requirements for influenza Vaccines (CPMP/BWP/214/96) and of the core SmPC/PL for inactivated seasonal influenza vaccines (CMDh/128/2003/Rev5 and CMDh/129/2008/Rev3)

Draft agreed by Vaccines Working Party	July 2013
Adopted by CMHP for release for consultation	25 July 2013
Start of public consultation	01 August 2013
End of consultation (deadline for comments)	31 October 2013

Comments should be provided using this template. The completed comments form should be sent to VWP@ema.europa.eu

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Explanatory note on the withdrawal of the note for guidance on harmonisation of requirements for influenza Vaccines (CPMP/BWP/214/96) and of the core SmPC/PL for inactivated seasonal influenza vaccines (CMDh/128/2003/Rev5 and CMDh/129/2008/Rev3)

1. Introduction

Twice a year, typically in February for the northern hemisphere and in September for the southern hemisphere, WHO experts meet to decide upon the influenza A and B virus strains that should be recommended for use in the production of influenza vaccine for the coming season. With the WHO recommendation being aimed worldwide, consideration needs to be given to the epidemiological situation of the European Union (EU) and the availability of strains that are suitable for vaccine manufacture. Consequently a meeting of EU experts is convened each year following the WHO northern hemisphere meeting in order to make an EU-wide decision regarding influenza virus strains for vaccine production.

For several decades Vaccine Manufacturers have been required to conduct small clinical trials with strain-updated seasonal influenza vaccines prior to each flu season and to present the results to Competent Authorities. The purpose of such trials was to verify:

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

Guidance for performing these clinical trials was given in the Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96), which also included details of Control Authority Batch Release of influenza vaccines process and requirements, labelling information and an Annex on Cell culture inactivated influenza vaccines (CPMP/BWP/2490/00).

As further described in the following sections, the above mentioned Note for Guidance and its Annex have been withdrawn as their content was considered outdated with respect to current understanding of critical elements of the annual strain update. Besides clarifying the reasons for the withdrawal, the present Explanatory Note aims at providing some guidance for the interim period, pending further recommendation from EMA.

This Explanatory Note does not affect the existing guidelines concerning pandemic influenza vaccines[1] or other vaccines (e.g. Guideline On Influenza Vaccines Prepared From Viruses With The Potential To Cause A Pandemic And Intended For Use Outside Of The Core Dossier Context (EMEA/CHMP/VWP/263499/2006); Guideline On Dossier Structure And Content For Pandemic Influenza Vaccine Marketing Authorisation Application (EMEA/CPMP/VEG/4717/2003- Rev.1); and Guideline On Clinical Evaluation Of New Vaccines (EMEA/CHMP/VWP/164653/2005)).

[1] For initial marketing authorisation application for any influenza vaccine, it is recommended to seek scientific advice.

2. Clinical requirements for yearly strain updates of seasonal influenza vaccines

The clinical immunogenicity trials so far requested in support of applications for annual strain updates in the context of seasonal vaccine use should no longer be routinely submitted[2] because based on the current knowledge they are not considered sufficiently informative on the expected efficacy and safety of the vaccine prior to approval of the annual strain change. This is also the conclusion of published studies and reviews that analyse the added value of the small clinical trials conducted in the context of annual strain update procedures[3].

The main reason for this is that the annual antigenic drift is unlikely to have a major impact on the immunogenicity profile of an inactivated or live attenuated vaccine so that its benefit/risk balance would be affected. Also from a safety perspective, the evidence provided by these trials is limited in the context of vaccines with an established profile.

A strengthened and sustainable monitoring of vaccine performance over the years is considered needed, which can be achieved by means of product-specific effectiveness studies and adequate plans to ensure active surveillance of vaccine safety. It is expected that these specific measures are included in the EU-RMP. The submission of effectiveness or safety surveillance data may not coincide with the annual update submission as it is not in principle a prerequisite for strains update. Relevant guidance on these aspects is under preparation.

3. Points to consider concerning quality requirements for yearly strain updates of seasonal influenza vaccines

With regards to the quality requirements for the annual update of seasonal influenza vaccines, applicants should refer to the draft Guideline on Influenza Vaccines, Quality Module (EMA/CHMP/BWP/310834/2012), the Procedural advice on the submission of variations for annual update of human influenza inactivated vaccines in the centralized procedure (EMA/CHMP/BWP/99698/2007 Rev. 2) and the CMDh Best Practice Guide on fast track procedure for the annual update of human influenza vaccines (CMDh/290/2013/Rev.0).

Control authority batch release of influenza vaccine

With regards to the Official Control Authority Batch Release of Seasonal Influenza Vaccines, applicants should refer to EDQM OCABR Network for Human Biological procedures and specific guidelines for influenza vaccines:

http://www.edqm.eu/en/Human-OCABR-Guidelines-1530.html#PSGVaccines

[2] This is without prejudice for the CHMP to request any additional data, including clinical data, if it becomes relevant due to exceptional circumstances.

[3] A.C.G. Voordouw et al., Evaluation of serological trials submitted for annual re-licensure of influenza vaccines to regulatory authorities between 1992 and 2002. *Vaccine* 2010

4. Core SmPC, PL and labelling for seasonal influenza vaccines

The CHMP and the CMDh agreed that the core SmPC and PL should be withdrawn from the CMDh website since the document is no longer useful or able to reflect all the available and emerging clinical data for individual influenza vaccines.

Further recommendation from EMA shall include a listing of the most relevant standard statements and warnings that can still be considered applicable to all influenza vaccines. Pending such update, any changes to SmPCs and PLs of seasonal influenza vaccines should be based on the available general guidance on the Product Information, such as the SmPC guideline, the Annex to guideline on clinical evaluation of new vaccines: summary of product characteristics requirements (EMEA/CHMP/VWP/382702/2006), and the QRD templates published on the EMA website.

Furthermore concerning the labelling, there should be clear information about influenza virus strains and season of use, since EU vaccines often contain virus strains which are related, but not identical, to those recommended by the WHO. This may cause confusion if some vaccine labels show the WHO strains and others show the actual vaccine strains.

The actual vaccine strains relevant for the European Union (i.e. those approved at the annual meeting of EU experts) will also be described in the dossier submitted for annual updates and in the production and test protocols.

In the SmPC, the season of use (e.g. 2012/2013) should be stated in section 2. The following statement should be used “This vaccine complies with the WHO (World Health Organisation) recommendation (northern hemisphere) and EU recommendation for the {year/year} season.”.

Information on small immediate packaging, outer/immediate packaging and package leaflet should comply with Directive 2001/83/EC and should also contain:

Small immediate packaging (section 1)	• season of use displayed as: “{year/year} season”
Outer/immediate packaging (section 2)	• WHO/EU recommended strains e.g. A/Victoria/361/2011 (H3N2) - like strain • season of use displayed as: “{year/year} season”
Package leaflet	• WHO/EU recommended strains followed by actual strains e.g. A/Victoria/361/2011 (H3N2) - like strain (A/Victoria/361/2011, IVR-165)) • The statement “This vaccine complies with the WHO (World Health Organisation) recommendation (northern hemisphere) and EU recommendation for the {year/year} season.” should be stated in section 6.