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Explanatory note on the withdrawal of the Note for guidance on harmonisation of requirements for influenza Vaccines and of the core SmPC/PL for inactivated seasonal influenza vaccines

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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 (i.e. when there was a change in vaccine composition) 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 is given in the Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96), which also includes 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).

EMA has initiated a number of activities to improve appraisal of influenza vaccines following the lessons learned from the 2009-2010 influenza A(H1N1) pandemic. In this context options to improve the appraisal of annual changes in the antigen composition of seasonal vaccines have been taken into account. As further clarified in the following section, the small annual clinical trials so far requested should no longer be conducted starting from the 2015-2016 influenza season. The above mentioned Note for Guidance CPMP/BWP/214/96 and its Annex (CPMP/BWP/2490/00) will be withdrawn by the end of 2014 as overall their content is considered outdated with respect to current understanding of critical elements of the annual strain update.

For the time being, the existing guidelines concerning pandemic influenza vaccines[1] or other vaccines are not varied (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)).

The re-appraisal exercise has been an opportunity to recognise the value of introducing further activities aimed at eliciting strengthened post-marketing monitoring of the benefit/risk profile of seasonal influenza vaccines. This document provides some guidance for the interim period, pending further recommendation from EMA.

[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 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 (applicable from the 2015-2016 influenza season) because based on the current knowledge they are not considered sufficiently informative of 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[2].

The main reason for the trial dismissal is that based on many years of safe and effective use in several million people i) from an efficacy perspective, the annual antigenic drift is unlikely to have a significant impact on the immunogenicity profile of an inactivated or live attenuated vaccine; ii) from a safety perspective, the level of evidence that can be obtained from such trials is limited. The manufacturing process for influenza vaccines undergoes only minor adaptations from year to year and the current evidence suggest that annual viral drifts per se are unlikely to radically modify the safety profile. Considering the above and also in light of the need to ensure timely availability of influenza vaccines every year, additional pre-approval clinical investigations are not considered needed.

3. New principles for seasonal influenza vaccines monitoring

The re-appraisal exercise mentioned in section 1 prompted the introduction of a strengthened and sustainable monitoring of vaccine performance over the years, which should be achieved by means of product-specific effectiveness studies and adequate plans to ensure enhanced surveillance of vaccine safety. These specific measures must be included in the EU-RMP, which should be in place for all influenza vaccines (i.e. both centrally and nationally authorised products, CAPs and NAPs). The submission of effectiveness study results or safety surveillance data does not need to coincide with the annual update submission as it is not a prerequisite for strains update. Relevant guidance on these aspects, including core requirements for safety surveillance and effectiveness studies (to be reflected in the RMP), is under preparation in the context of the influenza guideline revision and in the meantime early dialogue with EU Regulatory Authorities is encouraged.

New requirements for the 2014-2015 influenza season

Adequate plans to ensure enhanced safety surveillance of influenza vaccines should be in place as of the next influenza season 2014-2015. EMA will prepare and publish by March 2014 interim guidance on the principles for safety surveillance commitments that should be included in the 2014 annual strain update dossier. For CAPs and for NAPs that have an RMP, these pharmacovigilance activities are to be reflected in the RMP. For NAPs that do not have an RMP already in place, MAHs should contact National Competent Authorities for advice on how to submit safety commitments.

[2] 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. 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

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

The CHMP and the CMDh agreed that the core SmPC and PL (CMDh/128/2003/Rev5 and CMDh/129/2008/Rev3) 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.

Pending further guidance, any changes to SmPCs and PLs of seasonal influenza vaccines should be based as applicable 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[3].

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 World Health Organisation (WHO) 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”

[3] No requests for PI updates as a consequence of the withdrawal of the core SmPC or for other reasons are planned for the upcoming flu season 2014-2015.

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 World Health Organisation (WHO) recommendation (northern hemisphere) and EU recommendation for the {year/year} season.” should be stated in section 6.