22 March 2013
EMA/CHMP/BWP/99698/2007 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)

Procedural advice on the submission of variations for annual update of human influenza inactivated vaccines applications in the centralised procedure

Draft agreed by BWP	**March 2013**
Draft adopted by CHMP	March 2013
End of consultation (deadline for comments)	05 April 2013
Agreed by BWP	
Adoption by CHMP	
Date for coming into effect	

Keywords	***Human influenza inactivated vaccine, variation procedure, community annual strain update, fast-track, season***

Note 1: This procedural document currently applies only to inactivated vaccines. For quality aspects of technical requirements for annual strain update of live attenuated influenza vaccines see Annex I (variation application(s) content for live attenuated influenza vaccines) (EMA/CHMP/BWP/577998/2010)

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Procedural advice on the submission of variations for annual update of human influenza inactivated vaccines applications in the centralised procedure

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Executive summary

Seasonal influenza vaccines for human use authorised via the centralised procedure in accordance with Regulation (EC) No 726/2004, must be varied annually according to Article 18 of Commission Regulation (EC) No 1234/2008 and the Commission "Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 as well as on the documentation to be submitted pursuant to these procedures". This document describes the specific procedure, timelines and data requirements for the adoption of an opinion of such change(s) by the CHMP.

1. Introduction (background)

Every year, in general in mid February, a meeting of WHO experts takes place in Geneva, leading to a recommendation on the influenza A and B virus variants which should be used for the production of vaccine for the coming season worldwide. However, there remains flexibility within these recommendations to take into consideration the specificities of European Union epidemiological situation and adapt these recommendations as appropriate. In this respect, for instance, the European Medicines Agency (thereafter The 'Agency') publishes also yearly in their EU recommendation the use of reassortants for the manufacture of inactivated vaccines.

The EU recommendation regarding influenza virus strains for vaccine production for the next season is published further to the annual EU Ad Hoc influenza working party meeting which takes place at the Agency (usually mid/end of March, every year).

Further to the publication of the specific EU annual influenza virus strains, manufacturers start the production of each monovalent bulk(s). As soon as the reagents for standardisation are made publicly available by the WHO collaboration centres, the manufacturers will qualify monovalent bulks and will produce and release pilot/full scale of batches of the specific annual influenza vaccine for clinical trials. These clinical trials will start further to national regulatory clinical trial applications' approvals.

As soon as the quality documentation is available, the Marketing Authorisation Holder (MAH) will submit it to the Agency, so that the CHMP can assess it

If necessary, a request for additional data (e.g. clinical data) may be adopted during the assessment by the CHMP. Once the assessment is finalised, the CHMP will adopt an opinion which will be transmitted to the European Commission (EC) and the Marketing Authorisation Holder (MAH), as appropriate.

The timeframe of the procedure is defined in Article 18 of Commission Regulation (EC) No 1234/2008 (see further details of the procedure, timelines in section 4.1).

2. Scope

- This **procedural guidance document** concerns the **annual change in vaccine composition** (influenza A and B virus variants) of a centrally authorised seasonal influenza vaccine in order to meet the EU recommendations for human influenza virus strain(s) vaccine composition for the coming season.
- It provides guidance on the procedure, timelines and dossier content, MAHs should fulfil in order for the CHMP to issue its appropriate scientific opinion.

3. Procedure, Timelines and Marketing Authorisation(s) Content

3.1. Procedure and Timelines

3.1.1. General principles

The variation should be submitted by the applicant as a Type II variation as stated in the guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and will be processed under Article 18 of Commission Regulation (EC) No 1234/2008.

The content of the application is defined in section 3.2. No changes other than the ones related to the new strains used may be introduced in the Product Information.

Applicants are advised to consult the relevant aspects of the detailed post-authorisation procedural advice on the handling of variations as published in the Agency website, "Type II variations - Post-Authorisation Procedural Advice" http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000090.jsp&mid=WC0b01ac0580023398, as appropriate with regard to some practical aspects such as, number of applications, etc. and should make use of the European Variation Application Form as published in the NTA, Volume 2C.

The scope of the variation to be mentioned in the variation application form is "*annual update of Union Human influenza vaccine strain(s)".*

In principle, only the Rapporteur will be involved in the assessment of this specific variation aiming at updating the annual strain(s) of the Influenza vaccine in accordance with EU recommendations.

In accordance with Article 18 of Commission Regulation (EC) No 1234/2008, a **two step approach submission** is foreseen i.e. submission of the quality documentation, followed, where necessary, by the submission of additional data, e.g. clinical data.

First step: Maximum 45 days for CHMP assessment of data submitted, followed by either a CHMP opinion or a request for additional data which suspends the procedure (clock-stop). A Request for Supplementary Information (RSI) without suspending the procedure may be issued at D30.

Second step: Applicant is recommended to submit additional data within 12 days from the adoption of the request for additional data. Once the data are submitted, the procedure is restarted.

Maximum of 10 days for the CHMP to adopt its opinion, and within a maximum 3 days timeframe for the Agency to send this opinion to the European Commission and applicant. The Agency will update the relevant EPAR accordingly.

3.1.2. Details of the procedures

The details of the procedure are described below.

The Agency will take up to a maximum of 5 days for the validation of this application.

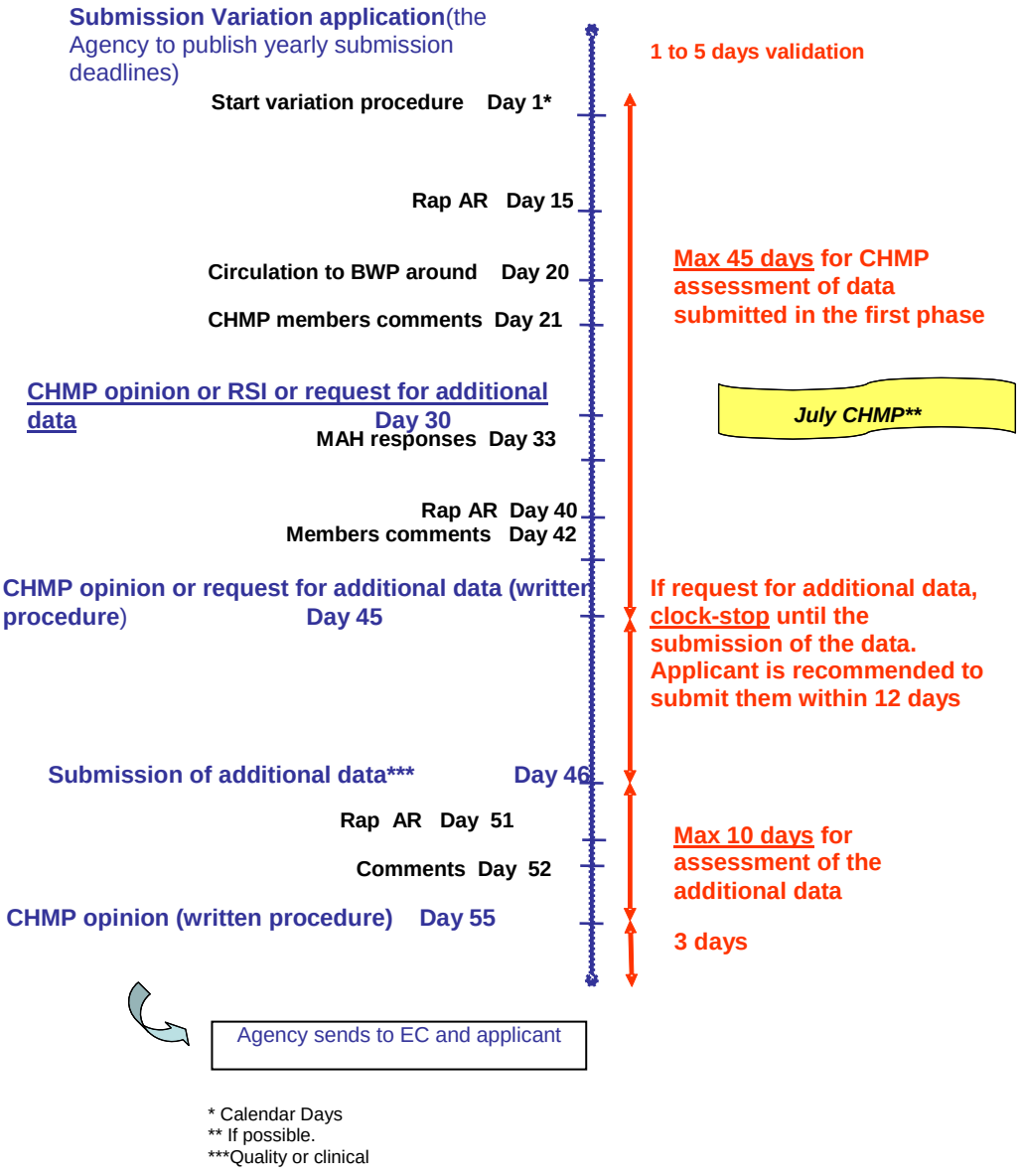
As only the strains are changed (and nothing else), no linguistic review of the product information is foreseen.

Once validated, the procedure will start (day 1) and the CHMP will have a maximum of 45 days to assess the quality documentation submitted. Where necessary, the CHMP may adopt a Request for Supplementary Information (RSI) without suspending the procedure at day 30 and this is scheduled to be done during the July CHMP meeting. In case the CHMP adopts an RSI, the MAH will be requested to provide the answers at day 33. The Rapporteur will have one week to prepare an updated AR and CHMP Members will have 2 days to comment. The adoption by the CHMP of an opinion or a request for additional data, e.g. clinical data concludes the first step of the procedure. In case a request for additional data is adopted, the procedure is suspended (clock-stop).

If a request for additional data has been adopted, the applicant is recommended to submit the requested data within 12 days. Upon receipt of this data, the procedure will restart and the an opinion will have to be adopted by the CHMP within 10 days, which will be subsequently transmitted to the EC and the applicant by the Agency within a maximum of 3 days. This will be followed by a Commission Decision to amend the terms of the marketing authorisation.

MAHs are advised to liaise with the Agency (i.e. PTL and Rapporteur) in advance of the submission of the variation, especially in view of possible deviation from the recommended deadlines.

Fast track procedure for community human influenza vaccines annual strain(s) update



* Calendar Days
** If possible.
***Quality or clinical

3.2. Variation Application(s) Content

IMPORTANT REMARK

Only changes related to the new strains used may be introduced. No other changes are allowed to be processed via the 'fast track' procedure.

3.2.1. First step submission – Quality

The variation should be submitted by the applicant as a Type II variation as stated in the guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and should contain the documentation described below. , by the **Agency recommended target annual deadline,** which will be **published every year together with the EU Annual strain(s) recommendations.**

The variation application should follow the EU recommendations of the Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) and should therefore include the following supporting documentation:

Module 1: - Administrative Information and Prescribing Information

1.0 Cover Letter
1.1 Comprehensive Table of Contents (not required if submitted in eCTD format)
1.2 Application Form (European Variation Application Form as published in the NTA, Volume 2C).
1.3 Product Information
1.3.1 SmPC, Labelling and Package Leaflet

> **Note: Only changes related to the strains used for the season may be introduced in these texts. The year of the season should not be part of the name of the medicinal product but should be included in section 1 of SmPC and corresponding sections of labelling. (At submission of the of variation application, the full set of annexes of the product information in all languages should be submitted to the Agency and MSs electronically in accordance with the CHMP members distribution list as published the Agency website).**

1.4 Information about the Quality Expert:
The relevant expert declaration(s) and signature must be provided, corresponding to the quality overall summary submitted in Module 2.

Module 2: Common Technical Document Summaries

2.1 CTD Table of Contents (Module 2 – 3) (not required if submitted in eCTD format)
2.2 CTD Introduction
2.3 Quality Overall Summary (addendum to "previous" Quality Overall Summary)

Module 3: Chemical-pharmaceutical and biological information for chemical active substances and biological products

Please note that only relevant and adequate sections of the CTD variation application should be submitted. All sections not felt to be necessary should however be justified adequately in the Summary/Overview.

3.2.S.2 Manufacture

3.2.S.2.3 Control of Materials
- seed lots: history:
- passage level
- characterisation of Haemagglutinin and Neuraminidase
- analytical protocols (including test results on seed lots)*

3.2.S.2.4 Control of Critical Steps and Intermediates

3.2.S.2.5 Process validation and/or evaluation
- monovalent bulks:
- manufacturing process strain specific changes
- validation of critical manufacturing steps (new strain)
    1. inactivation
    2. splitting efficiency

3.2.S.4.1 Specification (copy of approved specifications in a tabular format)

3.2.S.4.2 Analytical procedures

3.2.S.4.3 Validation of analytical procedures (validation of SRD test for new strains)

3.2.S.4.4 Batch analysis results of monovalent bulks: results (including test for neuraminidase) of the first three monovalent bulks from
- each working seed lot of a new master seed lot of new strains
- each working seed lot from previously approved master seed lot where the procedure of working seed lot preparation is different from the approved procedure

3.2.S.7 Drug Substance: Stability (Stability tests on the active substances: results from monovalent bulks where they are used for more than one year)

3.2.P.1 Composition

3.2.P.2.2.1 Pharmaceutical development: formulation development (actual formula (new season's strains) and Certificate of Analysis of batch(es) used in clinical trial(s) when available (either in quality or in clinical submission)

3.2.P.3.2 Batch formula (actual formula)

3.2.P.5.1 Specifications (Copy of approved specifications and routine tests analytical methods in a tabular format)

3.2.P.5.3 Validation of analytical procedures; validation of SRD test for new strains (either using trivalent bulk or drug product)

3.2.P.8 Drug Product: Stability
- Stability data from previous season
- Stability commitment(s)
- Post-approval stability protocol for the final lot Stability

**** Note:** Where the seed virus is tested for extraneous agents using PCR, and if further to discussion with the Agency and Rapporteurs the need for additional PCR testing of the seed has been agreed, these data should be included in this application.*

3.2.2. Second step submission –Additional data requested (e.g. clinical data)

Module 1: - Administrative Information and Prescribing Information

1.0 Cover Letter
1.1 Comprehensive Table of Contents (not required if submitted in eCTD format)
1.4 Information about the Expert(s):

The relevant expert declaration(s) and signature(s) must be provided, corresponding to the Summary submitted in Module 2.

Module 2: Common Technical Document Summaries

2.1 CTD Table of Contents (Module 2 – 5) (not required if submitted in eCTD format)
2.2 CTD Introduction
2.3 Quality Overall Summary (revised to first addendum to Quality Overall Summary, in case needed)
2.5 Clinical Overview
2.7 Clinical Summary

Module 5: Clinical study Reports

Please note that only relevant and adequate sections of the CTD variation application should be submitted. All sections not felt to be necessary should however be justified adequately in the Summary/Overview.

5.1 Table of Contents of Module 5 (not required if submitted in eCTD format)
5.2 Tabular listing of all clinical studies
5.3 Clinical Study Reports
5.3.6 Reports of Efficacy and Safety Studies

Note: Results of clinical studies with the new vaccine as required according to the Guideline Harmonization of requirements for influenza vaccines. These results are to be submitted as a short final report, including:

Raw data
Characteristics of the trial population (demography, co-morbidity, co-medication)
Standardised tables for immunogenicity and reactogenicity

Furthermore, confirmation should be included that the vaccine complies with CHMP requirements.
The type of serological test used should be stated clearly.
For further guidance see the above mentioned Guideline.
Finally, applicants are encouraged to include the following PSURs in the clinical data package (for eCTD submissions, a cross reference to the previous PSUR submissions is sufficient):
PSUR covering the period 1 September- 30 April of the previous season
PSUR covering the period 1 May - 31 August of the last but one season.

References (scientific and/or legal)

- Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the term of a marketing authorisation for medicinal products for human use and veterinary medicinal products.
- Communication from the Commission — Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01):

  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:017:0001:0044:en:PDF
- NTA Volume 2A, Procedure for marketing authorisation, Chapter 5 - Guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 as well as on the documentation to be submitted pursuant to these procedures :

  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:323:0009:0022:en:PDF
- NTA Volume 2B.
- Relevant section of the Agency post-authorisation procedural advice on the handling of variations as published in the Agency website, "Type II variations" - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000090.jsp&mid=WC0b01ac0580023398
- Core SPC for trivalent Influenza Vaccines, CMDh/128/2003/Rev3 September 2009.
- 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 (CPMP/BWP/2289/01).
- Adjuvants in Vaccines for Human Use (CHMP/VEG/134716/04).
- Pharmaceutical Aspects of the Product Information for Human Vaccines (CPMP/BWP/2758/02).
- Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97).