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

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. It will ultimately be updated to take also into consideration specificities of data and procedural requirements for live attenuated influenza vaccines.

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

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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 [1] 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 of 24 November 2008 as well as on the documentation to be submitted pursuant to these procedures" [2]. This document describes the specific procedure, timelines and data requirements for the adoption of an opinion of such change(s) by the CHMP, without jeopardising public health.

1. INTRODUCTION

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 wide decision 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 manufacturer/MAH will submit it to the Agency, so that the Rapporteur will initiate its review. In general, the Agency's Scientific Committee, the CHMP, should be able to adopt an opinion at its July plenary meeting or at the latest by written procedure within the timeframes defined in Article 18 of Commission Regulation (EC) No 1234/2008 (see further details of the procedure, timelines in section 4.1).

Once the clinical documentation is available, it is submitted to the Agency, which, further to the Rapporteur's assessment, will enable the CHMP to adopt its final opinion, which will be transmitted to the European Commission (EC) and the Marketing Authorisation Holder (MAH), as appropriate.

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[1] ***"Human influenza vaccines***

1. By way of derogation from Article 16, the procedure laid down in paragraphs 2 to 7 shall apply to the examination of variations concerning changes to the active substance for the purposes of the annual update of a human influenza vaccine.
2. The holder shall submit to the Agency an application containing the elements listed in Annex IV. If the application fulfils the requirements laid down in the first subparagraph, the Agency shall acknowledge receipt of a valid application and inform the holder that the procedure starts from the date of such acknowledgement.
3. Within 45 days following the acknowledgement of receipt of a valid application, the Agency shall give its opinion on the application.
4. Within the period referred to in paragraph 3, the Agency may request the holder to provide supplementary information.
5. The Agency shall submit forthwith its opinion to the Commission. The Commission shall, where necessary and on the basis of that opinion, adopt a decision on the variation to the terms of the marketing authorisation and inform the holder accordingly.
6. Where requested, the holder shall submit the clinical data and the data concerning the stability of the medicinal product to the Agency within 12 days from the expiry of the period referred to in paragraph 3. The Agency shall evaluate the data referred to in the first subparagraph and shall give its final opinion within 10 days following receipt of the data. The Agency shall communicate its final opinion to the Commission and to the holder within three days from the date of issue of its final opinion.
7. Where necessary and based on the final opinion of the Agency, the Commission shall amend the decision granting the marketing authorisation and update the Community Register of Medicinal Products provided for in Article 13(1) of Regulation (EC) No 726/2004 accordingly."

[2] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:323:0009:0022:en:PDF

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.
- The variation to be filed by the MAH will be a Type II variation in accordance with Article 18 of Commission Regulation (EC) No 1234/2008 and only the Rapporteur will be involved in the assessment of this variation.
- The scope of this variation is “annual update of Community Human influenza vaccine strain(s)”.

3. PROCEDURE, TIMELINES and MARKETING AUTHORISATION APPLICATION(S) CONTENT

3.1 Procedure and Timelines

3.1.1 General principles

MAHs 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“ - http://www.ema.europa.eu/pdfs/human/regaffair/4040410en.pdf, as appropriate with regard to some practical aspects such as, number of applications, etc.

MAHs are also strongly advised to contact the Agency PTL for further clarifications.

The applicant should make use of the European Variation Application Form as published in the NTA, Volume 2C.

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 with such procedure i.e. submission of the quality documentation first, followed, once available, but according to the maximum timelines of Article 18 of Commission Regulation (EC) No 1234/2008, by the clinical data (and if appropriate by the stability data) documentation:

First step: Maximum 45 days (Quality) for CHMP assessment/primary opinion adoption, followed by a

Second step: Maximum of 12 days (for the Clinical + Stability data, if appropriate, to be submitted by the MAH) followed by a

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

To fulfil the above legal steps and timelines, the Agency/CHMP will therefore accommodate the centralised variation procedure to include, if and as necessary, possible written procedures for either comments or adoption of certain opinion(s)/List of Questions (LoQs) and to involve the consultation(s) of the adequate working parties. However, the Committee will endeavour to have a plenary discussion/adoption, as appropriate, of the first step quality variation application submitted, during its July plenary meetings if possible.

MAHs should however be aware that any major objections identified during the assessment of the data submitted as part of either the "quality documentation" (which cannot be answered further to a potential 1st request for supplementary information by/at Day 45) or the clinical documentation could imply for the variation to be considered negative by the CHMP.

Furthermore no changes other than the ones related to the new strains used may be introduced in the Product Information.

3.1.2 Details of the Procedure

The procedure below describes all the different steps that should be followed to fulfil the legal requirements and timelines. The Agency will take up to a maximum of 5 days for the validation of this application.

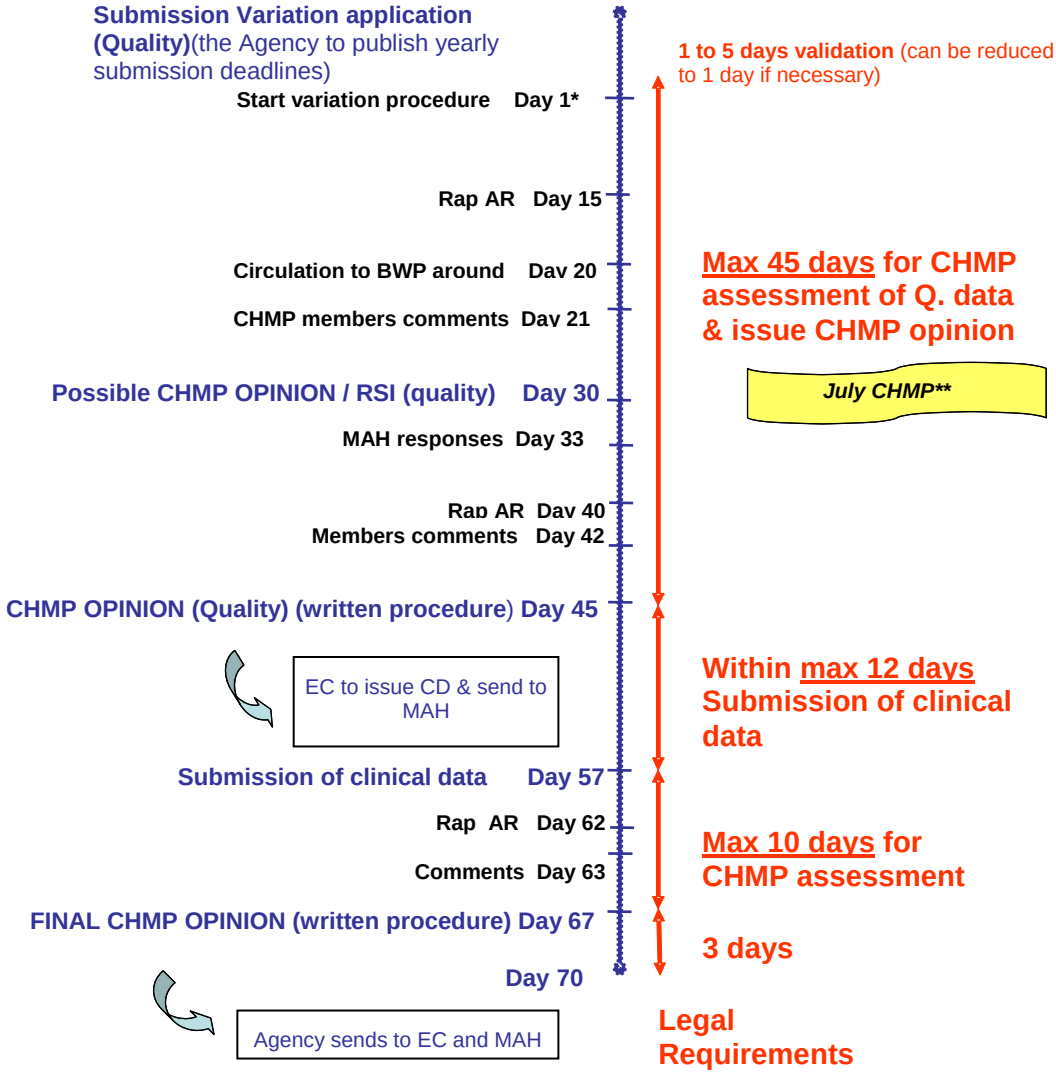
In principle, if with the quality variation application, only the strains are changed (and anything else), no linguistic review will be undertaken.

MAHs are strongly advised to discuss foreseen labelling changes to be introduced with the quality and/or clinical variation in advance of any of the variations submission to identify the adequate/appropriate linguistic review timetable.

Once validated, the procedure will start (day 1) and the Agency/CHMP will have a maximum of 45 days to issue its initial opinion on the quality documentation submitted. An adoption of a CHMP opinion or a Request for Supplementary Information (RSI) is foreseen at day 30 and this is scheduled to be done during the July CHMP meeting. In case the Committee 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.

Once the CHMP initial opinion on the "quality" documentation is adopted, it is transmitted to the EC to initiate the decision making process. Following the opinion on the quality data, the MAH has a maximum of 12 days to submit their clinical documentation to the Agency i.e. by day 57 of the overall procedure. Upon receipt of this data, the rapporteur will have a maximum of 10 days to prepare its AR and for the CHMP to adopt its final CHMP opinion which will be transmitted to the EC and MAH by the Agency within a maximum of 3 days. This will be followed by EC Decision Phase.

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



* Calendar Days
** If possible.

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" Variation Application

MAHs shall submit a Type II variation application containing the adequate **quality documentation** in accordance with Article 18 of Commission Regulation (EC) No 1234/2008, by the **Agency recommended target annual deadline,** which will be **published every year together with the EU Annual strain(s) recommendations.**

The current requirements for the content of the European application dossier are set out in Annex I to Directive 2001/83/EC, as amended.

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 (from European Variation Application Form as published in the NTA, Volume 2C).
1.3 Product Information
1.3.1 SPC, Labelling and Package Leaflet

Note: Only changes related to the new strains used may be introduced in these texts. The year of the season should not be part of the name of the medicinal product; it should be included in section 1 of SPC 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)
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
- seed lots: history:
  - passage level
  - characterisation of Haemagglutinin and Neuraminidase
  - analytical protocols (including test results on seed lots)*
- monovalent bulks:
  - manufacturing process strain specific changes
  - validation of critical manufacturing steps (new strain)
    1. inactivation
    2. splitting efficiency

3.2.S.2.3 Control of Materials
3.2.S.2.4 Control of Critical Steps and Intermediates
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 – "clinical" Variation Application

Module 1: - Administrative Information and Prescribing Information

1.0 Cover Letter
1.1 Comprehensive Table of Contents
1.2 Revised Application Form (from European Variation Application Form as published in the NTA, Volume 2C)
1.3 Product Information

1.3.1 SPC, Labelling and Package Leaflet

Note: No product information is expected to be submitted; if so, exceptionally details of the proposed changes and their justification should be clearly details with their rational in the cover letter and the clinical overview.

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)
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
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:

- **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. - (February 2010):

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/pdfs/human/regaffair/4040410en.pdf
- 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).