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Guideline on influenza vaccines – submission and procedural requirements

Regulatory and procedural requirements module - Draft

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This module will replace the procedural requirements of the following guidelines:

- Procedural advice on the submission of variations for annual update of human influenza inactivated vaccines applications in the centralised procedure (EMA/CHMP/BWP/99698/2007 Rev. 2)
- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (EMEA/CPMP/4986/03)

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

Keywords	***Submission and procedural requirements, influenza vaccines, inactivated, LAIV, seasonal, pre-pandemic, pandemic, annual strain update, pandemic strain update***

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Guideline on influenza vaccines – submission and procedural requirements

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1. Introduction (background)

The need to update the current guidelines regarding the development of influenza vaccines was recognised in the wake of the 2009-2010 influenza pandemic, as the Agency conducted its "*lessons learned*" exercise. Since then, experience has also been gained through the evaluation of scientific advice and marketing authorisation applications for influenza vaccines.

As announced in the Concept paper,[1] the revision of the guidelines on influenza vaccines has been organised with the aim of developing a consolidated influenza guideline that covers the regulatory, quality, non-clinical and clinical aspects of influenza vaccine development and dossier submission. The present module compiles with the regulatory and procedural requirements for the different types of influenza vaccines, in line with the scope described under section 2.

Subject to the eligibility criteria, marketing authorisation applications for influenza vaccines can be submitted either at centralised or national level. The centralised procedure is mandatory where the application falls within the scope of the Annex of Regulation (EC) No 726/2004, in particular where the vaccine virus has been prepared using one of the techniques mentioned in the Annex, e.g. reverse genetics.

This guideline lays down the procedural aspects related to the submission of marketing authorisation applications for influenza vaccines and subsequent updates of vaccine composition in the centralised procedure.

2. Scope

This module provides guidance on marketing authorisation applications and subsequent updates of vaccine composition for influenza vaccines in the centralised procedure to be used in seasonal, pre-pandemic or pandemic settings.

3. Legal basis and relevant guidelines

This module should be read in conjunction with Directive 2001/83/EC and its Annex I ; Regulation (EC) No 726/2004 ; Regulation (EC) No 1234/2008 and Chapter 5 of the Notice to Applicants.

This module should also be read in conjunction with the corresponding scientific guidelines on influenza vaccines and the European Pharmacopoeia.

4. Regulatory and procedural requirements for influenza vaccines

4.1. Seasonal influenza vaccines

This section provides an overview of the procedures that would apply to a marketing authorisation application (MAA) for this type of product and for subsequent strain changes.

[1] Concept paper on the revision of guidelines for influenza vaccines

4.1.1. Requirements for marketing authorisation application

A MAA for a seasonal influenza vaccine can be submitted to the Agency, upon confirmation of eligibility to the centralised procedure. For any seasonal vaccines manufactured by means of one of the techniques mentioned in the Annex of Regulation (EC) No 726/2004, e.g. reverse genetics, the use of the centralised procedure is mandatory.

Submission of a new seasonal vaccine is expected to be based upon a comprehensive dossier. The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

A standard evaluation process is intended to be followed, unless a request for accelerated assessment is justified by the applicant and accepted by the CHMP. Once adopted by the CHMP, the opinion is forwarded to the Commission for the decision-making process.

Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on the submission of centralised MAAs as published on the Agency website, with regard to practical aspects such as the number of applications or the fees.

4.1.2. Requirements for applications to change vaccine composition (seasonal strain update)

4.1.2.1. Selection of the seasonal strains in the EU

Seasonal influenza vaccines for human use authorised via the centralised procedure may be varied annually according to Article 18 of Regulation (EC) No 1234/2008 in order to update their strain composition in preparation for the influenza season.

Twice a year, typically in February for the northern hemisphere and in September for the southern hemisphere, WHO recommends the influenza A and B virus strains which should be used for the production of seasonal vaccine for the coming influenza season. However, there remains flexibility within these recommendations to take into consideration the specificities of the epidemiological situation in the European Union and to adapt these recommendations as appropriate. In this respect, the European Medicines Agency (hereinafter the 'Agency') publishes every year, usually in March, an EU recommendation, including the recommended reassortants for the manufacture of seasonal influenza vaccines.

Based on the EU recommendation, any strain replacements for authorised vaccines are approved via the procedure described in Section 4.1.2.2 (see section on seasonal strain update; quality and clinical modules of the influenza guideline).

4.1.2.2. Details of the procedure

The variation application should be submitted as a type II B.I.a.5 by the recommended target annual deadline, which will be published every year together with the EU annual strain(s) recommendations on the EMA website. The guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and the Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

The content of the application is defined in Annex I of this module. No changes other than the ones related to the new strains may be introduced in the product information.

Applicants are advised to consult the post-authorisation procedural advice on the handling of variations as published on the Agency website, with regard to some practical aspects such as the number of applications or the fees.

The scope of the variation to be mentioned in the variation application form is “annual update of Union human influenza vaccine strain(s)”.

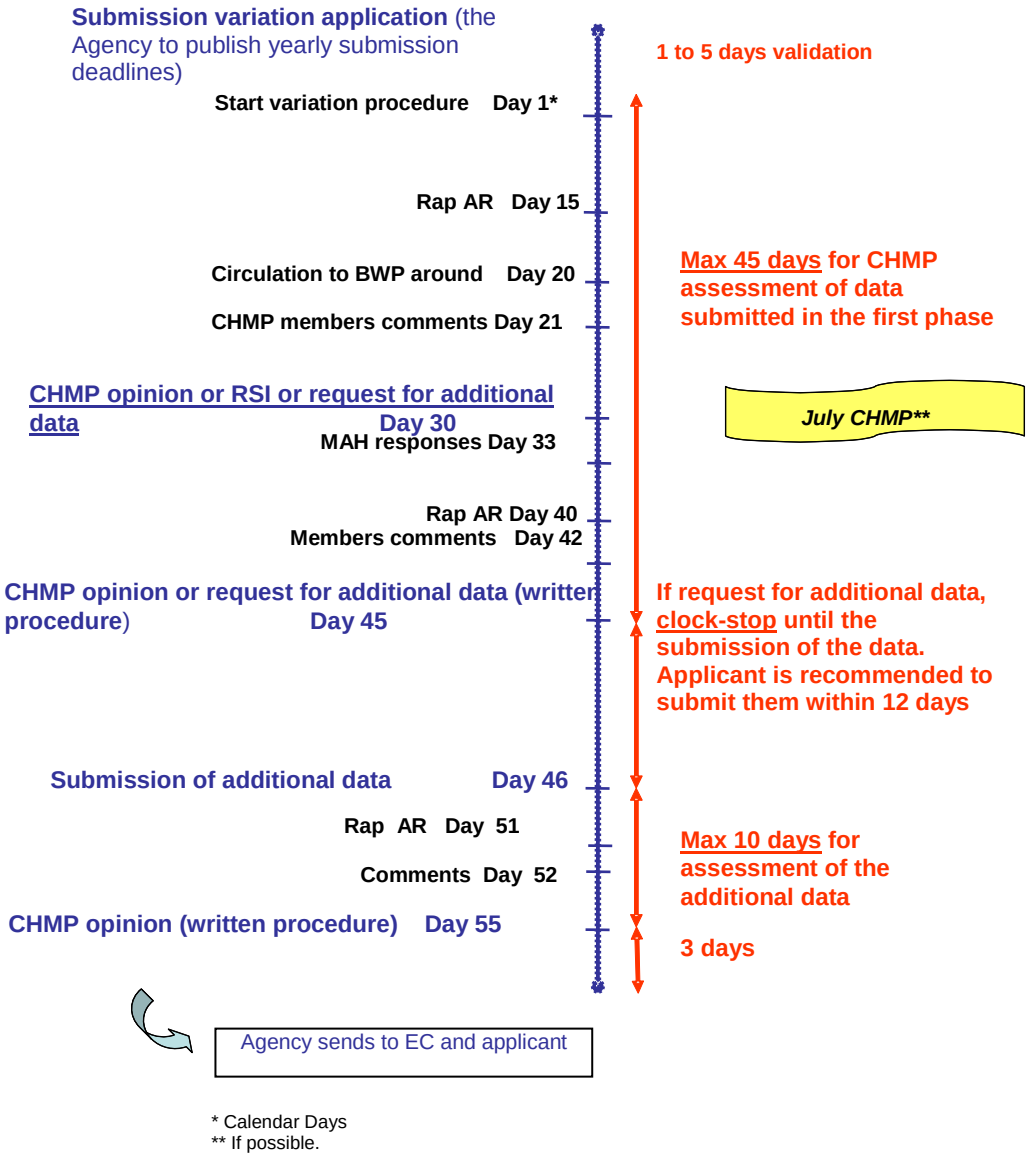
In accordance with Article 18 of Commission Regulation (EC) No 1234/2008, a ‘two step’ approach submission is foreseen i.e. submission of the quality documentation, followed, if necessary, by the submission of additional data:

- First step: within 45 days of the validation, the CHMP adopts an opinion to approve or refuse the variation application or the CHMP suspends the procedure (clock-stop) by adopting a request for additional data A request for supplementary information (RSI) without suspending the procedure may be issued at D30.
- Second step: where a request for additional data has been adopted, the marketing authorisation holder (MAH) is recommended to submit these additional data within 12 days from the adoption of the request for additional data. Upon receipt of this data, the procedure is restarted and the CHMP adopts an opinion within 10 days.

Within 3 days from the adoption of the opinion, the Agency sends the opinion to the MAH and the European Commission. This will be followed by a Commission decision to amend the terms of the marketing authorisation.

MAHs are advised to liaise with the Agency in advance of the submission of the variation, especially in view of possible deviation from the recommended deadlines.

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



4.2. Pre-pandemic (zoonotic) influenza vaccines

4.2.1. Requirements for marketing authorisation application for a pre-pandemic (zoonotic) influenza vaccine

Zoonotic influenza vaccines (also known as pre-pandemic vaccines) are intended for immunisation in the context of outbreaks of zoonotic influenza viruses with pandemic potential, including use when there is anticipation of a possible pandemic due to the same or a similar strain.

A MAA for a zoonotic influenza vaccine can be submitted to the Agency, upon confirmation of eligibility to the centralised procedure. For any zoonotic vaccines manufactured by means of one of the techniques mentioned in the Annex of Regulation (EC) No 726/2004, e.g. reverse genetics, the use of the centralised procedure is mandatory.

Submission of a new pre-pandemic vaccine is expected to be based upon a comprehensive dossier. The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

A standard evaluation process is intended to be applied, unless a request for accelerated assessment is justified by the applicant and accepted by the CHMP. Once adopted by the CHMP, the opinion is forwarded to the Commission for the decision-making process.

Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on the submission of centralised MAA as published on the Agency website, with regard to practical aspects such as the number of applications or the fees.

4.2.2. Requirements for applications to change vaccine composition (zoonotic strain change)

Replacement of the vaccine virus in a zoonotic influenza vaccine should be processed via a type II B.I.a.5 variation application.

The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

Applicants are advised to consult the relevant aspects of the post-authorisation procedural advice on the handling of variations as published on the Agency website, with regard to some practical aspects such as the number of applications or the fees.

4.3. Pandemic influenza vaccines

4.3.1. Marketing authorisation granted prior to the recognition of a pandemic situation ('pandemic preparedness vaccine')

In order to prepare for a pandemic situation, applicants are recommended to submit a marketing authorisation application for a pandemic vaccine containing a strain with pandemic potential (so-called 'pandemic preparedness vaccine').

This type of vaccine is based on the concept formerly known as 'mock-up' that mimics the future pandemic influenza vaccine in having the same manufacture and control and being of the same construct, notably the antigen content, excipients and adjuvant system.

The marketing authorisation application should be supported by a 'core pandemic dossier' including data on the potential pandemic strain(s) (see relevant modules for data requirements). When a pandemic situation is duly recognised by the WHO or the Union, the MAH should submit a variation application ('pandemic strain update') *as per* Article 21 of Regulation (EC) No 1234/2008 to include the declared pandemic strain in the pandemic vaccine ('pandemic strain update'). This variation will be reviewed under an accelerated timeframe.

'Pandemic preparedness vaccines' are indicated for immunization against potential pandemic strain(s) once an official pandemic declaration in the EU has been recognized and after that the variation to include the declared pandemic strain has been authorised.

4.3.1.1. Requirements for marketing authorisation application

Once eligibility to the centralised procedure is confirmed, the applicant can submit an application supported by a 'core pandemic dossier' which will include data on relevant strain(s) (see relevant modules for data requirements).

It is expected that a comprehensive dossier could not be generated outside a pandemic situation. A submission of a MAA based on a non-comprehensive dossier under the conditional marketing authorisation may therefore be considered if the applicant is likely to be in a position to provide the comprehensive clinical data after the declaration of a pandemic and if other requirements laid down in Regulation (EC) No 507/2006 are fulfilled ; an appropriate justification on the regulatory framework claimed, the type of data missing and whether these data could be generated should then be included in the dossier.

A standard evaluation process is intended to be applied, unless a request for accelerated assessment is justified by the applicant. Once adopted by the CHMP, the opinion is forwarded to the Commission for the decision-making process.

Applicants are encouraged to liaise with the European Commission before the grant of the marketing authorisation to request an exemption to the obligation to place the product on the Union market within three years (so-called 'sunset clause'). The MAH should provide a justification based on public health grounds and explaining the exceptional circumstances. A copy of the request should be addressed to the European Medicines Agency.

The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on the submission of centralised MAA as published on the Agency website, with regard to some practical aspects such as the number of applications.

Special fees incentives apply for applications based on a 'core pandemic dossier.' The Explanatory note on fees available on the Agency website should be consulted.

In case such application is envisaged, it is recommended to initiate discussions with competent authorities as early as possible.

4.3.1.2. Requirements for applications to change vaccine composition (pandemic strain change) during a pandemic situation

Where a pandemic situation is duly recognised by the WHO or the Union, a variation application may be accepted to include the declared pandemic strain in the pandemic vaccine ('pandemic strain update'), if appropriate.

As per Article 21 of Regulation (EC) No 1234/2008, it may be exceptionally and temporarily acceptable that certain non-clinical or clinical data are missing. In the latter, the MAH will have to submit the missing non-clinical and clinical data within the time limit set in the marketing authorisation.

The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on the handling of variations as published on the Agency website, with regard to some practical aspects such as the number of applications.

Special fees incentives apply for applications based on a 'core pandemic dossier'. The Explanatory note on fees should be consulted.

A pandemic variation will be assessed following an accelerated timetable. It is emphasised that an efficient interaction with the EMA Pandemic Task Force (ETF) to discuss critical issues in advance of the submission would be essential to allow acceleration of the variation procedure.

Once adopted by the CHMP, the opinion is forwarded to the Commission for the decision-making process which may be accelerated as appropriate.

The post-authorisation procedures to submit the missing data and to vary the terms of the marketing authorisation may be reviewed under an accelerated timeframe if appropriate.

4.3.2. Marketing authorisation submitted during a pandemic situation

4.3.2.1. 'Emergency procedure'

It may become necessary to authorise a new pandemic vaccine in a pandemic situation duly recognised by the WHO or the Union.

It is expected that it may be difficult to generate a comprehensive dossier at the time of the MAA. A submission of a MAA based on a non-comprehensive dossier under the conditional marketing authorisation may therefore be considered if the applicant is likely to be in a position to provide the comprehensive clinical data after the declaration of a pandemic and if other requirements laid down in Regulation (EC) No 507/2006 are fulfilled; an appropriate justification on the regulatory framework claimed, the type of data missing and whether these data could be generated should then be included in the dossier.

The Notice to Applicants, Volume 2B on the Presentation and format of the dossier Common Technical Document (CTD) should be followed.

If a MAA for a pandemic vaccine is submitted in such circumstances, the evaluation will be accelerated as appropriate.

Once adopted, the opinion will be forwarded to the Commission for the decision-making process, which will also be accelerated as appropriate.

Applicants are advised to consult the relevant aspects of the pre-authorisation procedural advice on the submission of centralised MAA as published on the Agency website, with regard to practical aspects such as the number of applications.

In case such application is envisaged, the applicant is recommended to initiate discussions with the competent authorities as early as possible.

4.3.2.2. Other routes of authorisation for a pandemic vaccine

In exceptional circumstances, depending on the emergency of the situation and where no 'pandemic preparedness vaccine' is already authorised for a specific vaccine construct, variations of a relevant

seasonal or pre-pandemic influenza vaccine, based on Article 21 of Regulation (EC) No 1234/2008, may be considered during a pandemic, if feasible from a regulatory and scientific perspective.

In case such an exceptional situation is envisaged, it is recommended to initiate discussions with competent authorities as early as possible, in particular to discuss the modalities and particulars of these applications.

5. Annex 1 – Seasonal strain change ('Annual update')

5.1. 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.

The variation should be submitted 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).

Please note that only relevant sections of the CTD corresponding to the supporting data for the variation application should be submitted. Any absence of a study/test report requires a justification in the appropriate summary/overview.

5.1.1. First step submission – quality

The supporting documentation described below should be included within the variation application. Any deviation (absence of data or additional data) should be justified and discussed with the competent authorities before the submission of the application.

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.

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

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.

5.1.2. Second step submission –additional data requested

Relevant sections of the CTD variation application should be submitted depending on the type of additional data submitted.

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), if appropriate
2.5 Clinical Overview (addendum to the previous Clinical Overview), if appropriate
2.7 Clinical Summary (addendum to the previous Clinical Summary), if appropriate

Module 3, 4, 5

To be submitted if additional data on quality, non-clinical* and/or clinical* data were requested.

** In principle, there is no need to provide clinical data to support seasonal strain updates. Vaccine performance should be monitored by means of product-specific effectiveness studies and enhanced safety surveillance. The reactogenicity profile of influenza vaccines after annual strain updates should be investigated in the population indicated for each vaccine (including children if applicable) in order to confirm acceptable tolerability of the newly recommended strain(s). For details, see Guideline on influenza vaccines, non-clinical and clinical module (EMA/CHMP/VWP/457259/2014).*