1. INTRODUCTION

Article 12 of Commission Regulation (EC) No 1234/2008 of 24 November 2008 as amended by Commission Regulation (EU) No 712/2012 of 3 August 2012, sets out the possibility for a special ‘fast track’ variation procedure for the annual change in active substance for the purpose of the annual update of a human influenza vaccine in order to meet the EU recommendation for human influenza virus strain(s) vaccine composition for the coming season.

For purely national marketing authorisations a comparable ‘fast track’ procedure is foreseen according to Art.13f of the Commission Regulation.

WHO recommends every year, in general in mid-February, the influenza A and B virus variants which should be used for the production of vaccine for the coming season worldwide. Taking into consideration the specificities of European Union epidemiological situation and adapting these recommendations as appropriate, the European Medicines Agency publishes further to the annual EU Ad Hoc influenza working party meeting (usually mid/end of March, every year) their EU recommendation for the use of reassortants for the manufacture of inactivated vaccines.

Because of the specificities inherent in the manufacture of human influenza vaccines the special ‘fast track’ procedure which accommodates the limited timeframe between the announcement of the WHO/EU on the virus strain(s) vaccines composition for the next season and the earliest availability of the vaccines (in summer), a ‘two-step’ procedure is foreseen for the annual variation i.e. submission and assessment of the variation application including the administrative and quality data (‘first step’), followed, if necessary, by the submission and assessment of additional data (‘second step’). However, if additional data are not deemed to be necessary/not requested by the RMS, the procedure will be finalised in ‘one step’.

As soon as the quality documentation is available, the MAH will submit the variation application including the administrative and quality data elements listed under section 4.1 of this Chapter. The assessment of these data starts immediately after the validation phase. If requested by the RMS, the MAH will submit the additional data in line with section 4.2 of this Chapter according to the timetable agreed with the RMS. The RMS provides only one final decision at the end of the procedure to the CMS for adoption.

Any other variations to human influenza vaccines other than the introduction of the annual strain update will follow the variation procedures foreseen in other sections of this Best Practice Guide.
The fast track procedure is specific for annual strain updates and cannot be combined/grouped with other variations.

The MAH’s are recommended to discuss the annual update submission including the need of additional data in advance (after publication of the EU recommendation for the use of reassortants) with the RMS or in case of purely nationally authorised products with the national competent authority.

This guidance takes into account the revision of the guidelines on influenza vaccines as announced in the respective Concept paper¹ and should be read in conjunction with the Guideline on influenza vaccines - quality module (EMA/CHMP/BWP/310834/2012) and the Guideline on influenza vaccines - non-clinical and clinical module (EMA/CHMP/VWP/457259/2014).

2. SCOPE

This guidance is aimed to facilitate the processing of the annual change in vaccine composition (annual change in vaccine composition (influenza A and B virus variants).

This guidance covers the ‘fast track’ procedure for MRP/DCP products. However, the same rules apply for purely nationally authorised products, except the commenting and adoption procedure by the CMSs.

This document provides guidance on the procedural steps, dossier content and timelines. It also provides guidance on labelling particulars (strain descriptions) in Annex III.

The ‘fast track’ procedure is a Type II Variation classified as B.I.a.5 “Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza” of 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.

This guidance is not applicable to the variations according to Article 21 of Regulation (EC) No 1234/2008. However, 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 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 on a case by case basis.

3. MRP VARIATION NUMBER

Information on the allocation of the MRP variation number is presented in Chapter 1 of the Best Practice Guides (BPGs) for the Submission and Processing of Variations in the Mutual Recognition Procedure (http://www.hma.eu/96.html).

4. CONTENT OF THE VARIATION APPLICATION

4.1 First step – Submission of the application

¹ Concept paper on the revision of guidelines for influenza vaccines
The MAH submits simultaneously to the RMS and CMS a Type II variation application containing the supporting documentation described below, presented in accordance with the appropriate headings and numbering of the EU-CTD format.

Please note that only relevant sections of the CTD variation application should be submitted. Any deviation (absence of data or additional data) should be justified in the relevant section of Module 3 and in the appropriate summary/overview and should be discussed with the RMS before 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 including MRP variation number;
1.3 Product Information;
1.3.1 Revised SmPC, Labelling and Package Leaflet;
   **Note**: Only changes related to the new strains used 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: CTD Summaries
2.1 CTD Table of Contents (Module 2 – 3) (not required if submitted in eCTD format);
2.2 CTD Introduction (update or addendum to previous CTD Introduction), if appropriate;
2.3 Quality Overall Summary (update or addendum to “previous” Quality Overall Summary).

Module 3: Quality documentation
This should be read in conjunction with the Quality Module (EMA/CHMP/BWP/310834/2012) for more detailed information.

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)²
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

² Where the seed virus is tested for extraneous agents using PCR, and if further to discussion with the RMS the need for additional PCR testing of the seed has been agreed, these data should be included in this application.
3.2.S.3 Characterisation (selection of characterisation studies e.g. particle size distribution, presence of aggregates etc.);
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 if clinical trial(s) has been requested to support the ‘annual’ update, Certificate of Analysis of batch(es) used in clinical trial(s) when available (either in the ‘first’ or ‘second step’ 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.

4.2 Second step – Submission of additional data (if requested)
When additional data are requested the MAH submits simultaneously to the RMS and CMS the relevant sections of the EU CTD variation application dossier depending on the type of additional 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: CTD Summaries
2.1 CTD Table of Contents (Module 2 – 5) (not required if submitted in eCTD format);
2.2 CTD Introduction (update or addendum to previous CTD Introduction), if appropriate;
2.3 Quality Overall Summary (update or addendum to previous Quality Overall Summary), if appropriate;
2.5 Clinical Overview (update or addendum to “previous” Clinical Overview), if appropriate;
2.7 Clinical Summary (update or addendum to “previous” Clinical Summary), if appropriate

Module 3, 4, 5
To be submitted if additional data on quality, non-clinical\(^3\) and/or clinical\(^3\) data were requested.

For purely national MA\(s\), the variation application has to be submitted to the relevant competent authority of the member state concerned including the same documents.

The submission of the variation to the RMS in the ‘first’ and in the ‘second step’, if required, should include the list of dispatch dates (all the dates of dispatch to the CMS) and declaration that the relevant national fees have been paid at the time of submission of the variation application.

RMS creates the CTS record to inform the CMSs about the start of the procedure.

5. AUTOMATIC VALIDATION

The automatic validation procedure described in Chapter 2 of the Best Practice Guides (BPGs) for the Submission and Processing of Variations in the Mutual Recognition Procedure (http://www.hma.eu/96.html) applies also for the application submitted in the ‘first step’ of the ‘fast track’ procedure, but with a shortened validation period of 7 calendar days.

6. START OF VARIATION PROCEDURE (Day 0)

Following the validation period the RMS completes the CTS record informing the CMS via CTS on the start and the timetable of the procedure, no additional email will be sent to the CMS\(s\). The MA\(h\) is informed by the RMS about the start date (Day 0) and timetable of the procedure.

7. EVALUATION

The Flow chart of the ‘fast track’ Type II variation procedure is provided in Annex II. As the ‘fast track’ procedure should be as flexible and short as possible the deadlines specified in the flow chart should be seen as maximum deadlines. It is strongly recommended that RMS and MA\(h\) agree prior to the submission of the variation on the timetable on a case by case basis. The fixed deadlines stipulated by the Variation Regulation as amended are highlighted in bold.

Once the application is validated the RMS has a maximum of 45 days to prepare a final variation assessment report (FVAR) and a decision on the application. The RMS may request the holder to submit additional data; in such a case, the RMS will inform the CMS. When a request for additional data is sent to the holder at the end of the ‘first step’ (see below), the ‘within 45 days’ period is stopped until the requested data has been submitted by the holder.

\(^3\) In principle, there is no need to provide non-clinical/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).
The RMS circulates its final variation assessment report (FVAR) and decision to the CMS. Within 12 days from the receipt the CMS shall adopt a decision accordingly and inform the holder and the RMS thereof. The main principles of the Type II Variation Procedure described in Chapter 5 of the Best Practice Guides (BPGs) for the Submission and Processing of Variations in the Mutual Recognition Procedure (http://www.hma.eu/96.html) apply also for the ‘fast track’ procedure, except the timetable.

7.1 First step

In practice the RMS will prepare and circulate a preliminary assessment report on the data submitted in the ‘first step’ (PVAR) to the CMS by the agreed date. The CMS send their comments as soon as possible but at the latest by the agreed date.

If the RMS or any of the CMS do not endorse the variation proposed by the MAH, the RMS will send a request for supplementary information (RSI) to the MAH and inform the CMS. The RMS should give a clear deadline (normally no longer than 7 calendar days) to the MAH for submitting the responses to the RSI. There is no clock stop foreseen for the submission of the response to the RSI within the ‘first step’.

After receiving the supplementary information from the MAH, the RMS prepares and circulates the final variation assessment report (FVAR) to all CMS for comments, and to the MAH for information. The CMS send their comments at the latest by the agreed date. If additional data are not necessary the RMS circulates its decision on the procedure together with the FVAR (if updated following CMS comments) and the final SmPC/PL/labelling at the latest by day 45 to the CMS and the MAH. The CMS should adopt the decision within 12 days and inform the holder and the RMS thereof. In the case of disagreement between the RMS and CMS, a breakout session can be arranged between day 45 and day 57 (e.g. by teleconference). The CMDh Best Practice Guide on Break-Out Sessions is followed.

If additional data are necessary the RMS requests the MAH officially for submission of these data (see Section 7.2).

7.2 Second step

This step is triggered only in case additional data are requested by the RMS.

The timeline (clock stop) for the submission of the additional data should be agreed by MAH and RMS on a case by case basis (submission is normally recommended within 12 days). The RMS informs the CMS accordingly.

Following receipt of the additional data the RMS restarts the procedure and informs the MAH and CMS via email about the timetable. The RMS circulates the FVAR on the additional data, a reference to the already agreed FVAR of the ‘first step’, the final SmPC/PL/labelling and its decision on the procedure at the latest by day 45 to the CMS and the MAH. The CMS should adopt the decision within 12 days and inform the holder and the RMS thereof. In the case of disagreement between the RMS and CMS, a breakout session can be arranged between day 45 and day 57 (e.g. by teleconference). The CMDh Best Practice Guide on Break-Out Sessions is followed.

8. OUTCOME

8.1 Acceptance of variation:
In the case where the variation is accepted (at the end of the ‘first step’ or in case of request for additional data at the end of the ‘second step’), the RMS will inform the MAH and CMSs that the variation is considered acceptable together with the date of acceptance. The RMS will update the CTS record. National approval of the variation should be issued within 7 calendar days.

8.2 Rejection:

In the case where the variation is rejected by the RMS and CMS, the RMS will inform the MAH and CMSs that the variation is considered rejected along with a description of the reasoning for the outcome. The MAH and CMS are informed of the outcome by email. The RMS will also update the CTS record, which should state the reasons for rejection.

Examples of suitable text for inclusion in the acceptance or rejection notifications issued to the MAH on completion of the procedure are included in Annex 1.
ANNEX I

Sample text for inclusion in the acceptance or rejection notifications issued to the MAH on completion of the procedure

Example 1

ACCEPTANCE OF VARIATION

The <<competent authority>> accepts the Type II variation for the annual update of the human influenza vaccine detailed in your application.

The following change has been notified:
<< enter change applied for>>

Example 2

REJECTION OF VARIATION

The <<competent authority>> rejects your Type II variation for the annual update of the human influenza vaccine, because of the following:
<<enter reason for non-acceptance>>
**ANNEX II**

As the ‘fast track’ procedure should be as flexible and short as possible the deadlines below should be seen as maximum deadlines. The finalisation of the procedure might be possible at earlier stages but depends on the specific procedure and should be agreed between RMS, CMS and MAH.

**II.1 ‘First step only’ procedure (no additional data requested)**

<table>
<thead>
<tr>
<th>Day 0</th>
<th>RMS starts the procedure after validation, completes the CTS record and sends an e-mail informing the MAH of the start date and timetable of the procedure. The CMS are only informed via CTS, there will be no additional mail. Start date should be set no more than 7 days after receipt of list of despatch.</th>
</tr>
</thead>
<tbody>
<tr>
<td>By Day 15</td>
<td>RMS circulates the PVAR to the CMS and to the MAH</td>
</tr>
<tr>
<td>By Day 21</td>
<td>CMS send their comments on the PVAR to the RMS</td>
</tr>
<tr>
<td>By Day 22</td>
<td>RMS sends the request for supplementary information (RSI) to the MAH and CMS. No clock stop</td>
</tr>
<tr>
<td>Days 23 to 29</td>
<td>Response of MAH to RSI</td>
</tr>
<tr>
<td>By Day 30</td>
<td>RMS circulates the FVAR to the CMS and MAH</td>
</tr>
<tr>
<td></td>
<td>RMS updates the CTS record</td>
</tr>
<tr>
<td>By Day 37</td>
<td>CMS send their final comments on the FVAR to the RMS</td>
</tr>
<tr>
<td><strong>By Day 45</strong></td>
<td>RMS circulates its decision on the procedure together with the FVAR (if updated following CMS comments) and the final SmPC/PL/labelling to the CMS and MAH</td>
</tr>
<tr>
<td><strong>Within 12 days</strong> (from the RMS decision)</td>
<td>CMS adopt the RMS decision and inform the RMS and MAH</td>
</tr>
<tr>
<td><strong>By Day 57</strong></td>
<td>Possible break-out meeting in case of disagreement</td>
</tr>
<tr>
<td></td>
<td>End of the procedure, the RMS notifies the completion of the procedure and, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS and the MAH</td>
</tr>
<tr>
<td></td>
<td>If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends</td>
</tr>
<tr>
<td><strong>Within 7 days</strong></td>
<td>National approval of the variation /new Marketing authorisation</td>
</tr>
</tbody>
</table>
## ANNEX II

### II.2 ‘Two step’ procedure (additional data requested)

<table>
<thead>
<tr>
<th>Submission</th>
<th>MAH submits variation application to the RMS and CMS and a list of dispatch dates to the RMS only. RMS creates the CTS record.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0</strong></td>
<td>RMS starts the procedure after validation, completes the CTS record and sends an email informing the MAH of the start date and timetable of the procedure. The CMS are only informed via CTS, there will be no additional mail. Start date should be set no more than 7 days after receipt of list of despatch.</td>
</tr>
<tr>
<td>By Day 15</td>
<td>RMS circulates the PVAR to the CMS and to the MAH.</td>
</tr>
<tr>
<td>By Day 21</td>
<td>CMS send their comments on the PVAR to the RMS.</td>
</tr>
<tr>
<td>By Day 22</td>
<td>RMS sends the request for supplementary information (RSI) to the MAH and CMS. No clock stop.</td>
</tr>
<tr>
<td>Days 23 to 29</td>
<td>Response of MAH to RSI.</td>
</tr>
<tr>
<td>By Day 30</td>
<td>RMS circulates the FVAR to the CMS and MAH. RMS updates the CTS record.</td>
</tr>
<tr>
<td>By Day 37</td>
<td>CMS send their final comments on the FVAR to the RMS.</td>
</tr>
<tr>
<td>By Day 37</td>
<td>RMS requests MAH officially to submit additional data. RMS and MAH agree on the timeline for submission of the data on a case by case basis (normally within 12 days). Clock stop.</td>
</tr>
<tr>
<td>Clock off period</td>
<td>Until MAH submits additional data according to the agreed timeframe.</td>
</tr>
<tr>
<td><strong>Day 38</strong></td>
<td>RMS restarts procedure and informs the MAH and CMS via email about the restart and the timetable.</td>
</tr>
<tr>
<td><strong>By Day 45</strong></td>
<td>RMS circulates the FVAR on the additional data, a reference to the already agreed FVAR of the ‘first step’, the final SmPC/PL/labelling and the RMS decision on the procedure to the CMS and MAH.</td>
</tr>
<tr>
<td><strong>Within 12 days</strong> (from the RMS decision)</td>
<td>CMS adopt the RMS decision and inform the RMS and MAH.</td>
</tr>
<tr>
<td><strong>By Day 57</strong></td>
<td>Possible break-out meeting in case of disagreement. End of the procedure, the RMS notifies the completion of the procedure and, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS and the MAH. If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends.</td>
</tr>
<tr>
<td><strong>Within 7 days</strong></td>
<td>National approval of the variation /new Marketing authorisation.</td>
</tr>
</tbody>
</table>
Annex III

Labelling requirements

NCAs and manufacturers are requested to follow the labelling examples given here for strain descriptions. The examples are based on seasonal influenza vaccines, however the approach is also applicable to pandemic preparedness vaccines and zoonotic vaccines – if such vaccines are nationally authorised. The translation of the word ‘-like’ should be one word/ a succinct translation. The term ‘-derived strain’ should not be used in place of ‘-like strain’.

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

<table>
<thead>
<tr>
<th>Small immediate packaging (section 1)</th>
<th>Outer/immediate packaging (section 2)</th>
<th>Package leaflet</th>
</tr>
</thead>
<tbody>
<tr>
<td>• season of use displayed as: “{year/year} season”</td>
<td>• WHO/EU recommended strains, e.g.:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A/Victoria/361/2011 (H3N2) - like strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• B/Brisbane/60/2008 – like strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• B/Phuket/3073/2013 – like strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• A/California/7/2009 (H1N1)pdm09 – like strain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• season of use displayed as: “{year/year} season”</td>
<td>• WHO/EU recommended strains followed by actual strains, e.g.:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A/Victoria/361/2011 (H3N2) - like strain (A/Victoria/361/2011, IVR-165)⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• B/Brisbane/60/2008 – like strain (B-Brisbane/60/2008, wild type)⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• B/Phuket/3073/2013 – like strain, (B/Utah/9/2014, wild type)⁶</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A/California/7/2009 (H1N1)pdm09 – like strain (A/Christchurch/16/2010, NIB-74)⁷</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 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.</td>
</tr>
</tbody>
</table>

---

⁴ Example describes the case whereby the reassortant is derived from the recommended wild-type
⁵ Example describes the case whereby the wild-type is used as the vaccine strain
⁶ Example describes the case whereby the vaccine strain is derived from a wild-type antigenically like the recommended strain
⁷ Example describes the case whereby the reassortant is derived from a wild-type antigenically like the recommended strain
- WHO/EU recommended strains followed by actual strains, e.g.:
  - A/Victoria/361/2011 (H3N2) - like strain (A/Victoria/361/2011, IVR-165)\(^8\)
  - B/Brisbane/60/2008 – like strain (B-Brisbane/60/2008, wild type)\(^9\)
  - B/Phuket/3073/2013 – like strain, (B/Utah/9/2014, wild type)\(^10\)
  - A/California/7/2009 (H1N1)pdm09 – like strain (A/Christchurch/16/2010, NIB-74)\(^11\)
  - 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 2.

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\(^8\) Example describes the case whereby the reassortant is derived from the recommended wild-type

\(^9\) Example describes the case whereby the wild-type is used as the vaccine strain

\(^10\) Example describes the case whereby the vaccine strain is derived from a wild-type antigenically like the recommended strain

\(^11\) Example describes the case whereby the reassortant is derived from a wild-type antigenically like the recommended strain