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NOTICE TO APPLICANTS

A GUIDELINE ON

FAST TRACK PROCEDURE FOR HUMAN INFLUENZA VACCINES

MAY 1999

This guideline will be included in The Rules governing Medicinal Products in the European Community
The Notice to Applicants Volume 2C Regulatory Guidelines

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GUIDELINE

"Fast track procedure for human influenza vaccines"

Changes to a marketing authorisation for human influenza vaccines

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Procedural guidance for mutual recognition of the "Annual variation human influenza vaccines":

This procedural guidance concerns the annual change in vaccine composition in order to meet the EU recommendations for human influenza vaccine composition for the coming season. A mutual recognition application for such a change follows a special variation procedure, the so called "fast track procedure".

The procedure for processing annual variations for human influenza vaccines is outlined with respect to:
- action to be taken by the Reference Member State;
- action to be taken by the Concerned Member States;
- action to be taken by the Applicant.

1 Action by the Reference Member State (RMS)

Administrative/Quality part of the variation
The administrative/quality data include SPC, patient leaflet, labelling and the chemical, pharmaceutical and biological documentation.

	-	Inform applicant of MR procedure variation number on request of MA-holder.
	-	Receive admin/quality part of application with fee.
	-	Receive from applicant a fax with despatch dates of the variation application when despatch is complete and statement that the relevant national fees have been paid.
	-	Validation (Check for correct fee, application form, supporting data, amended documents).
	-	Complete Eudratrack record
	-	Notify CMS of the intended procedure start date (the start date should be set no more than 5 working days after receipt of fax with despatch dates).
Day 0	-	Notify applicant and CMS of start date if no notification of an invalid application has been received from CMS by the intended start date or if CMS indicates that the application is valid after earlier notification of invalid application.
	-	Indicate CMS a date (up to day 15) by which a preliminary variation assessment report (VAR) on admin/quality part will be available.
	-	Assess admin/quality part of variation application.
By Day 15	-	Circulate preliminary VAR on admin/quality part to CMS.
	-	Set date for comments (at least 6 days after circulation of preliminary VAR on admin/quality part).
By Day 21	-	Receive any contribution from CMS for inclusion in VAR on admin/quality part or supplementary information request.
By Day 22	-	Send one request for supplementary information as appropriate (no clock-off period) to applicant and inform CMS. If no objections have been raised, the admin/quality part can be considered acceptable and this part of the variation application can be finalised (see By Day 42 under Agreement)
Days 23 to 29	-	Receive applicant's response.
	-	Consider response. Where serious issues arise, contact other RMS of

similar annual variations of influenza vaccines.

By Day 30	-	Circulate final VAR on admin/quality part to CMS with draft decision.
By Day 37	-	Receive notification of position of CMS.
		If no notification of disagreement with draft decision of RMS has been received, this part of the variation can be finalised (see By Day 42 under Agreement)
Days 37 to 42	-	Reach agreement with CMS.
By Day 42		**Agreement** between Member States on admin/quality part:
	-	Notify CMS of the outcome;
	-	Formal national approval or refusal of admin/quality part of variation notified to applicant.
		Disagreement between Member States:
	-	Refer to EMEA for CPMP arbitration;
	-	Notify CMS and applicant concerning referral.

Clinical part of the variation

By Day 54	-	Receive clinical part of application (at the latest 12 days following the decision by day 42 on the admin/quality part of the dossier).
	-	Notify applicant and CMS of receipt and indicate a date (up to day 61) by which a Variation Assessment Report (VAR) on the clinical part will be available.
Days 54 to 60	-	Assess clinical part of variation application.
	-	Receive notification of invalid application from CMS, if applicable.
By Day 61	-	Circulate VAR on clinical part to CMS with draft decision.
By Day 64	-	Receive notification of position of CMS.
		If no notification of disagreement with RMS has been received, the variation can be finalised (see By Day 68 under Agreement)
Days 64 to 68	-	Reach agreement with CMS.
By Day 68		**Agreement** between Member States on clinical part:
	-	Notify CMS of outcome of variation procedure;
	-	Formal national approval or refusal of variation notified to applicant.*

*National approval of the variation or the new Marketing Authorisation should be issued within 5 working days further to the approval of the fast track procedure.

Disagreement between Member States:

- Refer to EMEA for CPMP arbitration;

- Notify CMS and applicant concerning referral.

2 Action by the Concerned Member States (CMS)

If in the course of the procedure, a CMS raises a question which they consider to pose an obstacle to the mutual recognition of the decision to be taken, reference shall be made without delay to the provisions of Article 15, last paragraph, of Directive 75/319/EEC (referral for binding arbitration).

Administrative/Quality part of the variation
The administrative/quality data include SPC, patient leaflet, labelling and the chemical, pharmaceutical and biological documentation.

	-	Receive admin/quality part of variation completed with the MR procedure variation number and with fee.
	-	Receive from applicant a fax with despatch dates of the variation application when despatch is complete and statement that the relevant national fees have been paid.
	-	Validation (Check for correct fee and language requirements).
	-	Notified of intended procedure start date by RMS.
	-	In exceptions, where there is a problem, request applicant to rectify problem and notify RMS of invalid application by intended start date via Eudratrack. As soon as problem has been solved, inform RMS of valid application by updating the Eudratrack record. Notify applicant.
Day 0	-	Notified of procedure start date by RMS and date by which the preliminary variation assessment report (VAR) on admin/quality part will be available.
By day 15	-	Receive preliminary VAR on admin/quality part from RMS.
By day 21	-	Send any contributions to RMS for inclusion in VAR or request for supplementary information.
By day 22	-	Receive copy of request from RMS for supplementary information.
		If no objections have been raised, the admin/quality part can be considered acceptable and this part of the variation application can be finalised (see By Day 42 under Agreement)
Days 23 to 29	-	Receive additional data from applicant.
By day 30	-	Receive finalised VAR on admin/quality data from RMS.
By day 37	-	Notify RMS of position on VAR decision.
		If no CMS has notified RMS of disagreement with draft decision, this part of the variation can be finalised (see By Day 42 under Agreement)
Days 37 to 42	-	Discussion with RMS, as requested.

By day 42		**Agreement** between MS on admin/quality part:
	-	Receive notification of outcome from RMS
	-	Formal national approval or refusal of admin/quality part notified to applicant
		Disagreement between Member States:
	-	Receive notification of referral from RMS
	-	Involvement in binding arbitration.

Clinical part of the variation

By day 54	-	Receive clinical part of application (at the latest 12 days following the decision by day 42 on the admin/quality part of the dossier)
	-	Notified by RMS of date by which VAR on clinical part will be available.
Days 54 to 60	-	Notify RMS of invalid application, if applicable.
By Day 61	-	Receive VAR on clinical part from RMS.
By Day 64	-	Notify RMS of position on VAR decision.
		If no CMS has notified RMS of disagreement with draft decision, the variation can be finalised (see By Day 68 under Agreement)
Days 64 to 68	-	Discussion with RMS, as requested.
By Day 68		**Agreement** between MS on clinical part:
	-	Receive notification of outcome of the variation procedure from RMS
	-	Formal national approval or refusal of variation notified to applicant. * *National approval of the variation or the new Marketing Authorisation should be issued within 5 working days further to the approval of the fast track procedure.
		Disagreement between Member States:
	-	Receive notification of referral from RMS
	-	Involvement in binding arbitration.

3 Action by applicant

a) General approach

Because of the specificities inherent in the manufacturing of human influenza vaccines, a special 'fast track' Type II variation procedure is applicable for the annual variation. This 'fast track' procedure consists of two steps. The first part concerns the assessment of the admin/quality data (SPC, patient leaflet, labelling and the chemical, pharmaceutical and biological documentation). The second part concerns the assessment of the clinical data.

To initiate a 'fast track' Type II variation procedure, the EC application form "Application for Variation to a Marketing Authorisation" should always be used. The application form should be completed taking into account the guidance notes for the completion of the application form for variation to a marketing authorisation - see Section 7 of this chapter. The correct MR procedure variation number should be mentioned on the application form. The applicant should ask the RMS for this number when informing the RMS of the intended submission date.
The correct number of copies of the completed application form and the supporting data, in the appropriate languages (see Chapter VII), and the correct fee should be despatched to the RMS and each of the CMS, preferably simultaneously. A cover letter should be included with each application form, and this should indicate: the product name in each CMS (including the RMS), the marketing authorisation holder's name and address in each CMS (including the RMS). The supporting data should consist of the following:

First part of the procedure

Administrative data
Revised SPC, labelling and patient leaflet. Only changes related to the new strains used may be introduced in these texts.
Furthermore, the applicant may wish to change the product name to include the new relevant annual season.

Chemical-pharmaceutical-biological data
A revised chemical-pharmaceutical-biological expert report or an addendum to the current expert report. Furthermore, the following data are required.

II A1. Composition of the medicinal product
II A3. Clinical trial formula(e): actual formula (new season's strains)
II B1. Manufacturing formula: actual formula
II C1.1. Copy of approved specifications in a tabular format
II C1.3. Manufacturing process:
- 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

II C1.4 Specific quality control testing: validation of SRD test for new strains
II C1.6. Batch analysis results (monovalent bulks): results of the first three monovalent bulks from

each working seed lot of new strains (including test for neuraminidase)
II E1. Copy of approved specifications and routine tests analytical methods in a tabular format
II F1. Stability tests on the active substances: results from monovalent bulks where they are used for more than one year
II F2. Stability tests on the finished product: results from the previous vaccine
Commitment to report stability data of new vaccine if outside specifications
II F3. Annual stability testing protocol.

Second part of the procedure

Clinical data
A revised clinical-pharmacological expert report or an addendum to the current expert report.
Furthermore, 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 (using the models supplied, see Annex I).

Furthermore, confirmation should be included that the vaccine complies with CPMP 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.

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

It is important to be aware that although a number of CMS may elect to notify the applicant of the following, only the RMS is actually required to do this:

- clock start dates
- requests for supplementary information

The RMS will forward these notifications only to the address of the company stated on the application form forwarded by the applicant. It is essential that this office copies this notification to each of their relevant offices in the other CMS.

If a variation application is to be withdrawn, this may only be done in advance of the initiation or trigger of arbitration proceedings and the application must be withdrawn simultaneously from all member states.

b) Specific approach

1. Inform RMS of intended submission date and ask for MR procedure variation number (to be filled in on application form). The submission date is recommended to be not later than 20 June in order to obtain approval ultimately on 3 September.

2. Ensure that the supporting data are complete.

3. Reference to the EC *Guideline on the Variation Assessment Report* may be useful.

4. The application should be despatched to the RMS and each of the CMS, preferably simulataneously.
   Fax in a single document to the RMS and CMS all the despatch dates of the variation application when despatch is complete and include statement that the relevant national fees have been paid.

5. In exceptions, where CMS request invalid application to be rectified, liaise with RMS if necessary and respond immediately. Notify RMS of response.

6. The RMS will advise the applicant of the clock start date.

7. Within 22 days of the clock start date, the RMS may require the applicant to submit supplementary information on the admin/quality data.

8. The supplementary information on the admin/quality data should be sent simultaneously to RMS and each of the CMS, preferably within a few days but within 7 days of request.

9. Between days 37 and 42, the RMS will liaise with the applicant if a divergent position between member states or refusal is likely. The applicant has the opportunity to withdraw the variation at this stage from all Member States.

10. Not later than 12 days after the decision on the admin/quality part of the dossier, submit the clinical part simultaneously to the RMS and each of the CMS (by day 54).

11. Between days 64 and 68, the RMS will liaise with the applicant if a divergent position between member states or refusal is likely. The applicant has the opportunity to withdraw the variation at this stage from all Member States.

12. On or before 68 days of the clock have elapsed the applicant will be advised that the application is either approved or refused or that it has been referred for arbitration.

13. The applicant will receive formal approval or refusal of the variation from the RMS and all CMS.

14. If approval, the decision will be implemented in each Member State within 5 working days further to the approval of the fast track procedure unless specific issues.
    Please note that in some Member States a new marketing authorisation will be issued.