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GUIDELINE ON SUBMISSION OF MARKETING AUTHORISATION APPLICATIONS FOR PANDEMIC INFLUENZA VACCINES THROUGH THE CENTRALISED PROCEDURE

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1. INTRODUCTION

Manufacturers/Applicants of influenza vaccines have the choice to submit the *core pandemic dossier* and its subsequent *pandemic variation* either to the EMEA for a centralised approval, or to National Competent Authorities for a National/Mutual Recognition Procedure approval.

However, where the pandemic influenza strain has been prepared using one of the techniques mentioned in 'list A' of the Annex to Council Regulation (EEC) 2309/93, e.g. reverse genetics, the use of the centralised system is obligatory.

This guideline lays down the procedure to Manufacturers/Marketing Authorisation Applicants (MAAs) and Marketing Authorisation Holders (MAHs) on issues associated with the submission, and approval of a core pandemic dossier during the inter-pandemic period, followed by a fast track approval of the pandemic vaccine, based on the submission of a pandemic variation via the centralised procedure.

This guideline should be read in conjunction with the Guideline on dossier structure and content for marketing authorisations for pandemic influenza vaccines (EMEA/CPMP/VEG/4717/03) and any other relevant guidelines related to the development of vaccines.

2. LEGAL FRAMEWORK

Directive 2001/83/EC, as amended, lays down in Article 8 the requirements for a marketing authorisation application and Council Regulation (EEC) 2309/93, lays down the procedure for submission to the EMEA via the centralised route.

Commission Regulation (EC) 1085/2003 lays down in Article 8 the requirements for the variation of a marketing authorisation in a pandemic situation with respect to human diseases, via the centralised route.

3. SETTING UP OF TASK FORCE GROUPS

In order to increase the preparedness of both the industry and competent authorities for a possible influenza pandemic, different task force groups will be set up.

3.1. Joint EMEA-Industry Task Force (JEIF)

This task force will consist of the following participants:

- CPMP representatives, who will be the rapporteurs and co-rapporteurs for the core dossier (once they are appointed),
- VEG-experts,
- Members of the Ad-Hoc Influenza Working Party,
- Members of the Inspectorate Working Party and/or GMP inspectors from the supervisory authorities.
- OMCL/EDQM representative(s) involved in the official batch release of influenza vaccines,
- European Commission representatives (DG Enterprise and DG Sanco),
- Manufacturers of pandemic influenza vaccines[1],

[1] Once the core dossier is submitted/approved, this will be the Marketing Authorisation Applicant (MAA) or Marketing Authorisation Holder (MAH). MAAs or MAHs are encouraged to bring along representatives from the manufacturing facilities.

- Representative(s) from WHO,
- EMEA staff.

This group should, ideally, be set up before the submission of the core pandemic dossier.

This JEIF will meet on a regular basis[2] and will:
- provide information and advice to regulatory authorities (EMEA, MRFG, national authorities, Commission services)
- discuss quality, preclinical and clinical aspects with authorities which are common to all manufacturers
- contribute to the development or revision of any additional regulatory guidance in the area of pandemic influenza vaccines
- review the status of preparedness of vaccine manufacturers

3.2. EMEA Task Force (ETF)

This task force will consist of the following participants:
- Rapporteurs and co-rapporteurs for the core dossier,
- VEG experts,
- OMCL representative(s),
- European Commission representatives (DG Enterprise and DG Sanco),
- EMEA staff.

This task force can be supplemented with additional experts and representatives, such as Members of the Inspectorate Working Party and/or GMP inspectors from the supervisory authorities and representatives from WHO.

This group should be set up in parallel with the submission of the core-pandemic dossier or, at the latest, during the interpandemic period not later than in phase 0 level 3.

The task of the ETF will include:
- provide information and advice to Regulatory authorities (EMEA, MRFG, National Authorities, Commission services),
- interactions with the manufacturers, including ongoing scientific discussions prior to the submission of the pandemic variation dossier (see point 5.1),
- discussion of post-authorisation data (see point 7).

3.3. Evaluation Project Team (EPT)

This task force will consist of the following participants:
- Rapporteur and co-rapporteur appointed for the specific dossier and their assessment teams,
- VEG experts,
- European commission representative (DG Enterprise),
- EMEA Staff.

This group will be set up at the same time of the submission of the core pandemic dossier, and is product specific.

[2] During the interpandemic period, it is proposed to have yearly meetings. It is proposed that this meeting takes place adjacent to the yearly influenza strain selection meeting of the Ad-hoc Influenza working party.

The EPT will be involved in the fast track assessment of the pandemic variation (see point 5.2)

4. SUBMISSION AND EVALUATION OF THE CORE PANDEMIC DOSSIER

The core pandemic dossier should be submitted in CTD format in accordance with the requirements laid down in the European Commission Notice to Applicants, Volume 2B - Common Technical Document (CTD) together with any other relevant guidelines.

The Applicant is advised to contact EMEA for a pre-submission meeting as early as possible to facilitate the submission of the core pandemic dossier and as such refer to the pre-submission guidance document on the EMEA website (www.emea.eu.int) and highlight in advance of the meeting any specific points for discussion.

With regard to fees, any request for fee waiver should be addressed to the EMEA Executive Director.

This application will be processed through a standard centralised procedure with consultation with its relevant working parties (e.g. the Vaccine Expert Group (VEG)). An opinion from the CPMP will be issued and followed by a European Commission Decision[3]. Discussions on the product information (SPC, Labels and PL) will be part of the licensing procedure of the core pandemic dossier. Therefore, during the pandemic variation (see section 6), the need to updating the product information will be minimum[4]. Once the Commission Decision is issued, the EMEA together with the MAH will prepare a European Public Assessment Report (EPAR) which will be published on the EMEA Website.

This mock-up influenza vaccine may be marketed after a pandemic situation occurs and after a variation application containing all relevant information on the specific pandemic vaccine strain has been filed[5].

Once the Marketing Authorisation is granted, variations resulting from any changes to the original data submitted i.e. manufacturing changes, maintenance activities, Periodic Safety Updates etc. should be submitted to the EMEA.

5. PANDEMIC SITUATION – STEPS BETWEEN THE AUTHORISATION OF THE CORE PANDEMIC DOSSIER AND INITIATION OF THE FAST TRACK PANDEMIC INFLUENZA VARIATION

5.1. Proposed actions in advance of the announcement of a Influenza Pandemic[6]

All steps for actions taken by WHO are described in Annex 1.

[3] What is considered a 'mock-up' vaccines for the core pandemic dossier is stipulated clearly in the Guideline on dossier structure and content for marketing authorisations for Pandemic Influenza vaccines. Clinical data from the current interpandemic influenza strains cannot be used in the core pandemic dossier and manufacturers are required to develop a mock-up vaccine and to test it in clinical trials.

[4] Finalising the discussion on the product information at the time of the core pandemic dossier authorisation will greatly reduce the time for assessment of the pandemic variation. The product information approved in the core pandemic dossier authorisation will normally not have to change (except for some information on the pandemic strain) when the pandemic variation is submitted.

[5] Unless if the mock-up vaccine strain has the same antigenic composition as the pandemic vaccine strain. In such situation, the mock-up vaccine will be marketed after the announcement of the influenza pandemic.

[6] Announcement of an influenza pandemic will be done by WHO or European Commission in the framework of Decision 2119/98/EC.

Actions at the level of the EMEA[7] and at the level of the manufacturers of pandemic influenza vaccines will have to be initiated as soon as possible. This means, where possible, before the confirmation of a pandemic (phase I). See also Figure 1 for a schematic representation of this procedure.

a) At the level of the EMEA:

As soon as possible after the announcement of *Phase 0 – preparedness level 3*, a meeting of the JEIF should be held. Individual sessions with the different manufacturers need to be organised for confidentiality reasons. Depending on the speed and spread of the pandemic, this JEIF meeting might take place before or immediately after the announcement of the pandemic.

Issues to be discussed at this meeting include, but are not limited to the following:
- identification of the manufacturers of pandemic vaccines. This may include a discussion of capacity of production,
- availability of vaccine reference viruses and reagents,
- availability of all starting materials for the production of pandemic influenza vaccines (for egg derived vaccines, the availability of fertilised hens' eggs needs to be confirmed),
- any pending manufacturing issues which would benefit discussion with the authorities,
- GMP inspection relation issues,
- status of the authorisation of the core dossier,
- time lines for submission of pandemic variation,
- status report on the official release testing of the pandemic influenza vaccine batches: the (draft) OMCL procedure[8] foresees the possibility of official batch release in parallel with QC testing of the final product by the manufacturer. The OMCL will have to keep the task force informed of the status of individual discussion between the MAH and the OMCL/EDQM.
- agreement on a plan for the submission of status reports by the MAHs and ongoing scientific discussions with the task force.

b) At the level of the manufacturers:

In Phase 0 – preparedness level 3, or earlier if possible, WHO intends to distribute vaccine reference viruses[9]. Although the official recommendation for composition of the pandemic vaccines will only be made by the WHO / CPMP at the beginning of Phase 1, manufacturers should start the preparation of seed lots from these reference viruses when available.

[7] This document does not cover the actions taken or to be taken by the national health authorities in the event of an influenza pandemic. These are described in National or EU Pandemic Influenza preparedness plans, and are broader than the actions to be taken by the EMEA. Such actions include issues such as availability and distribution of the vaccine and surveillance.

[8] A draft OMCL procedure for the batch release in the event of an emergency situation (PA/PH/OMCL (2002) 46, 2R) was released for consultation in May 2003.

[9] WHO will initiate the work to develop and evaluate candidate strains for the production of vaccines against the novel influenza strains during Phase 0 – preparedness level 1 or 2. The time to produce a suitable strain will vary from 1 week (if a non pathogenic, antigenically identical, virus strain is available) to 3 months (if reassortants have to be made). Virus strains prepared using reverse genetics can be prepared in circa 3 weeks, but may need 1-2 months of safety testing.

5.2. Proposed actions after the announcement of a pandemic influenza until the submission of a pandemic variation

All actions below must take place as soon as possible after the announcement of Phase 1 of the Influenza pandemic.

a) Proposed actions at the levels of the EMEA:
   - WHO will announce the antigenic composition of the pandemic influenza strain. It is possible that WHO will also recommend a virus strain representative for the strain causing the pandemic. As soon as possible after this announcement, a CPMP-Ad hoc Influenza working party meeting should be held to recommend the strain to be used for the production of pandemic influenza vaccines for use within the EU. Ideally, the CPMP should publish its strain recommendation within 48 hours of the WHO announcement. This is likely to require a meeting with the influenza specialists in the different EU member states via video or telephone link and an adoption of the recommendation by the CPMP via a written procedure.
   - It is proposed to have an open dialogue with the MAHs during the initial steps of the development and manufacture of the pandemic Influenza vaccine, to allow discussion of critical issues. This dialogue will result in a scientific view from the EMEA Task Force (ETF), facilitating the assessment and the fast-track approval of the pandemic variation. The scientific views of the ETF will be recorded in a 'Task Force Report' which will be provided to the MAH, and which can be attached to the pandemic variation. Therefore, regular task force meetings will be organised with the individual manufacturers during the initial months of the pandemic[10].
   - As soon as the submission time of a pandemic variation is known, the EMEA will organise a meeting of the Evaluation Project Team (EPT) for a fast-track assessment of the submitted variation application.

b) Proposed actions at the level of the Manufacturers:
   - Manufacturers will have received candidate influenza strains in Phase 0, preparedness level 3 (see above), or as soon as available thereafter.
   - They will adapt the vaccine strain to the manufacturing process (if necessary) and will establish and test the seed lots.
   - Vaccine antigen conformity lots will be prepared and tested.
   - During development and manufacture of the conformity lots, the MAH might propose to have (a) meeting(s) with the ETF.
   - Vaccine batches will be prepared and tested.
   - The official batch release of vaccine batches could be initiated in parallel with release testing by the manufacturers. Practical agreements with the OMCL should be finalised as soon as possible after the announcement of the influenza pandemic.
   - The MAH will prepare the pandemic variation and submit it to EMEA and the rapporteur/co-rapporteur for evaluation. Manufacturers should inform the EMEA at least 1 week in advance of the anticipated date of submission of the pandemic variation.

[10] The manufacturers have indicated that they would need between 9 and 18 weeks to have the first lots of vaccine available. The timeline depends on the need to adapt the virus strain for growth in the different cell substrates. The Guideline on dossier structure and content for pandemic influenza vaccine marketing authorization application provides the opportunity to speed up the initial steps of the manufacturing process (i.e. testing of the seed lots).

6. SUBMISSION AND EVALUATION OF THE PANDEMIC VARIATION

Article 8 in Commission Regulation (EC) No 1085/2003, provides for a variation to the terms of the Marketing Authorisation for human influenza vaccines to be accepted after an application has been received by the Agency.

The pandemic variation application should be submitted in CTD format in accordance with the requirements lay down in the European Commission Notice to Applicants, Volume 2B - Common Technical Document (CTD) together with any other relevant guidelines.

6.1. Assessment phase

The aim is to have a fast-track assessment of the submitted variation. The assessment will include all normal steps (assessment report, list of questions, assessment of responses) and will lead to an opinion by the CPMP. The intention would be to limit this assessment phase to 2-3 days. However, this short timeframe will only be feasible if there has been a good dialogue with the ETF and critical issues have been discussed in advance of the submission pandemic variation, as described above (see section 5.2.a). If this dialogue has not taken place, a longer assessment phase might be needed.

The variation application will not be extensive, as it might not contain non-clinical or clinical data[11], and only those quality data that are specific to the pandemic influenza vaccine. The pandemic variation should be similar in size to that of a type II variation application and not a full application. In addition, some of the critical issues might already have been discussed with the ETF (see above).

The following is a proposal on how this fast track assessment might be organised:

Day 1:

- The EPT meets (either at the EMEA or virtually[12] via telephone or video link) to agree on strategy and start the assessment of the variation
- The company representatives should be available (at the EMEA or via telephone/video link) to respond to any issues that might arise during assessment (minor issues for clarification that do not require a formal list of question).
- If the variation is acceptable (if necessary with appropriate commitments), the rapporteur/co-rapporteur will prepare their joint assessment report. An opinion on the Pandemic variation will be prepared by the EMEA secretariat.
- If the ETP identifies information to be provided, the MAH is expected to provide the requested data not later than lunchtime of Day 2.

Day 2:

- If no questions have been raised, the rapporteur/co-rapporteur joint assessment report will be formally agreed by the ETP.
- If additional information has to be provided by the MAH, this information will be assessed. The company might be asked for further clarifications of minor outstanding issues. The rapporteur/co-rapporteur will prepare their joint final

[11] Within the Core dossier – pandemic variation concept [as described in the Guideline on dossier structure and content for pandemic influenza marketing authorisation application (EMEA/VEG/4717/03)], the requirement to submit clinical safety and efficacy data as inscribed in Article 8 of Regulation (EC) No 1085/2003 is fulfilled by the commitment to collect immunogenicity, effectiveness and safety data of the pandemic vaccine during the actual pandemic and to report these results to the Authorities.

[12] Travel restrictions might apply during an influenza pandemic.

assessment report and an opinion on the pandemic variation will be prepared by the EMEA secretariat.

Day 3:

- The rapporteur/co-rapporteur joint final assessment report will be formally agreed by the ETP.

6.2. CPMP approval

On day 2 or 3 (see above) the joint assessment report or joint final assessment report, together with the draft opinion, the Letter of Commitment[13] from the company and the proposed text for the EPAR update, will be forwarded to the CPMP members via electronic means. The frequency of PSUR submission during the influenza pandemic needs to be agreed with CPMP prior to approval of the Pandemic variation.
Formal adoption by the CPMP should take place within 24 hours.
After 24 hours, the opinion and assessment report are forwarded to the Commission for the marketing authorisation decision.

6.3. EPAR update

The EPAR will be updated immediately after the Commission Decision for the pandemic variation[14].

7. POST AUTHORISATION FOLLOW-UP

The pandemic variation will be approved with the commitment to accumulate immunogenicity, effectiveness and safety data of the pandemic vaccine during use.

Facilities for rapid sharing of these data with all EU competent authorities should be in place since the information will likely have implications for all vaccines in use in the pandemic.

If during the initial assessment of these post-authorisation data by the rapporteur and co-rapporteur important signals arise, the ETF[15] should meet to consider if this would necessitate changes in the vaccine, in the vaccination schedule or programme.

The advice from the ETF will be forwarded to the CPMP for adoption and an appropriate regulatory action will be taken. This might be the identification of the need for a variation to amend the pandemic marketing authorisation or the product information to be submitted by the MAH, and an expedited review of such a variation might be agreed by the CPMP.

[13] Commitments relate to quality aspects (if necessary) and to the provision of safety and effectiveness data gathered during use of the vaccine during the Influenza pandemic. A frequent submission of PSUR data (e.g. monthly) might be requested.
[14] A template will be developed on the information which need to be provided in the EPAR update after the pandemic variation approval.
[15] In view of the worldwide implications, it is proposed that also representatives from WHO join the ETF.

WHO ALERT LEVELS ON AN INFLUENZA PANDEMIC

The WHO has defined different *alert levels* in relationship to an influenza pandemic[16]:

Phase 0 is the inter-pandemic period, when occasional outbreaks raise concern about the possibility of a pandemic. The following levels of preparedness are defined by WHO:

- Preparedness level 1: isolation of a novel virus subtype from a single human case, without clear evidence of spread of such a virus
- Preparedness level 2: confirmation that two or more human infections have occurred with a new virus subtype, but without confirmation of human to human transmission
- Preparedness level 3: Human to human transmission confirmed

Phase 1: confirmation of the onset of the pandemic. The pandemic will be declared when the new virus subtype has been shown to cause several outbreaks in at least one country and to have spread to other countries with consistent disease patterns indicating that serious morbidity and mortality is likely in a least one segment of the population. Depending on the amount of early warning, this phase may or may not have been preceded by the above-described series of increasing levels of preparedness.

Phase 2: Regional and multi-regional epidemics

Phase 3: End of the first pandemic wave

Phase 4: Second or later waves of pandemic

Phase 5: End of the pandemic

[16] See following website: http://www.who.int/emc-documents/influenza/docs/index.htm/sec3.htm

FIGURE 1