European Medicines Agency

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Pandemic influenza and avian influenza vaccines: status of EMEA activities

Introduction

1. This Note addresses the EMEA activities related to Human Pandemic influenza vaccines and Avian influenza vaccines for birds.

Human pandemic influenza vaccines

Background

2. Since mid-2003, the EMEA has been involved in European Pandemic Influenza Preparedness planning activities.
3. In 2003-2004, the Vaccine Expert Group developed guidelines on pandemic influenza vaccines, which defined scientific issues (dossier requirement)[1] and procedural aspects for the authorisation of such vaccines via the centralised procedure[2]. They introduced the principle of "core dossier"[3]. Both guidelines were published on the EMEA Website in April 2004.
4. The Agency also reviewed antivirals for use during an influenza pandemic, including the extemporaneous preparation and stability of such formulations. The CHMP review of quality, safety and efficacy of such antivirals was published on the EMEA Website in October 2005[4].
5. In 2005, EMEA worked together with DG Sanco on incentives for the vaccine manufacturers to develop pandemic influenza vaccines (Public Private Partnership proposal[5]).

Current situation

6. "Core dossiers" will result in Marketing Authorisations, which may then be varied to include the pandemic strain of virus when it is available.
7. Recognising the need to have systems in place in the Agency to deal with the review of such variations, or indeed non-core dossiers should they be submitted, the EMEA has developed a Pandemic Influenza Crisis Management Plan, which addresses policy, strategy and procedures for:
    - Accelerated evaluation and authorisation of pandemic influenza vaccines (via centralised procedure);
    - Post-authorisation follow-up of centrally authorised pandemic influenza vaccines and antivirals;
    - Responding to safety signals from non-centrally authorised antivirals or from use of bulk active substance of centrally authorised, antivirals.

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[1] Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application. http://www.emea.eu.int/pdfs/human/vwp/471703en.pdf

[2] Guideline on Submission of Marketing Authorisation Applications for Pandemic Influenza Vaccines through the Centralised Procedure. http://www.emea.eu.int/pdfs/human/vwp/498603en.pdf

[3] The concept of a "core dossier" allows the evaluation and approval of an application based on a 'mock-up vaccine' (with pandemic-like influenza strain) to be completed in the interpandemic period. At the time of the influenza pandemic, only a limit amount of new data on the actual pandemic strain will have to be submitted as a variation to the "core dossier". The evaluation period for the pandemic variation will be extremely short (less than 1 week, after submission of data, which will be reviewed on a "rolling basis").

[4] Summary report – review on influenza antiviral medicinal products for potential use during pandemic http://www.emea.eu.int/pdfs/human/pandemicinfluenza/33997205.pdf

[5] http://europa.eu.int/comm/health/ph_threats/com/Influenza/influenza_key03_en.pdf

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8. The Plan is supported by a Pandemic Process Map, which covers steps from submission of applications for pandemic influenza vaccines through to post-authorisation. It also includes work instructions and lists of necessary contact details. Communication policy aspects are addressed in the Plan.
9. The plan has been published on the EMEA Website for consultation, and observations and comments received from the vaccine manufacturers are currently being reviewed.
10. The final Pandemic Influenza Crisis Management Plan to the CHMP at their March meeting. Additional work instructions related to pharmacovigilance and post authorisation aspects of antivirals to be used during an influenza pandemic will be included.
11. Training sessions for assessors from Member States and EMEA staff involved in the review of dossiers and a simulation exercise to test the effectiveness of the plan and work instructions will be undertaken.
12. EMEA is working with the vaccine manufacturers on the pandemic plan and has regular meetings to monitor the progress on submission of "core dossiers" and matters relevant to an influenza pandemic: the *Joint EMEA-Industry Task Force* meeting will meet in the last week of March 2006.
13. EMEA is continuing to work in close collaboration with the European Commission (DG Sanco and DG Enterprise), ECDC and WHO on all the aspects related to pandemic influenza.

EMEA experience with core dossiers

14. The EMEA core dossier approach is being accepted widely, even outside of Europe (e.g. Canada and Australia are applying the same principle).
15. EMEA is actively promoting the development of pandemic influenza vaccines by:
    - Allowing full fee waivers[6] / deferrals[7] for core dossiers, including for scientific advice on core dossier;
    - CHMP agreeing in principle, in October 2005, to the fast-track scientific advice and accelerated review of core dossiers for pandemic influenza vaccines.
16. EMEA has received two applications for core dossiers[8,9] and the evaluation of these dossiers has started in January 2006. Both applications are following an accelerated review, which could result in an opinion as of April/May 2006, provided no major issues arise during assessment.
17. A further 1-2 core dossiers are anticipated to be submitted in 2006, and further core dossier submissions are announced for 2007.

<u>Avian influenza vaccines for birds</u>

18. The CVMP considered at its November 2005 meeting appropriate action in relation to avian influenza vaccines in view of the absence of any authorised vaccines and noted that Article 3 of Regulation (EC) No 726/2004 allows for such avian influenza vaccines to be submitted via the centralised procedure. The Committee considered recommendations to the Commission could be made in 3 areas:
    - Development of conditions for an accelerated procedure and possibilities of authorisations under exceptional circumstances
    - Minimum data requirements for avian influenza vaccines
    - Need to coordinate vaccine approval and approval of accompanying diagnostic assays in case a "vaccinate to live" policy would be considered
19. The Chairman of the CVMP wrote to the Commission on 17 November 2005 informing of the proposals and requesting a mandate and clarification of the scope for CVMP.
20. The Commission wrote to the Chairman of CVMP on 5 December and informed that the proposals would be discussed in particular with DG Sanco.

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[6] Decision of Executive Director March 2005 (EMEA/93746/2005)
[7] Council Regulation (EC) No 1905/2005 – 14th November 2005
[8] http://www.emea.eu.int/pdfs/general/direct/pr/42591605en.pdf
[9] http://www.emea.eu.int/pdfs/general/direct/pr/3532206en.pdf

- As a short term action the CVMP was requested to start establishing the minimum data requirements for avian influenza vaccines to be used in accordance with Article 16 of Council Directive 92/40 for the control of Avian Influenza.
- In the medium term CVMP was encouraged to work with the Commission to analyse the possibilities offered by the new pharmaceutical legislation and if appropriate further develop a specific legal framework for evaluation of avian influenza vaccines.
- The approval of accompanying diagnostic assays if a "vaccinate to live policy" is adopted was considered a long-term action.

21. At the request of the Commission a meeting of the Chief Veterinary Officer's representatives on 10 January 2006 was attended by a number of CVMP representatives and the EMEA. This meeting was a working group on vaccination against avian influenza and part of the meeting was attended by industry representatives. At this meeting the urgent need for authorised vaccines against avian influenza was confirmed.
22. At the January CVMP meeting there was a further discussion on necessary action in relation to avian influenza. A letter was then sent to the Commission emphasising the need for legislative amendments to the Directive which could be dealt with by the review of Annex I, the importance for avian influenza vaccines to be centrally authorised in order to aid a harmonised approach and the need for incentives to the industry such as fee waivers and an accelerated procedure.
23. A drafting group, consisting of members of the CVMP's Immunologicals Working Party, met at EMEA on 30 January 2006 to discuss the minimum data requirements for avian influenza vaccines.
24. A further meeting was convened in Brussels on 31 January 2006 attended by representatives of EMEA, CVMP, DG Enterprise, DG Sanco, DG Research and both avian influenza manufacturers as well as IFAH-Europe. The meeting concluded that there was a need to
    1. amend the current legislation, in particular making use of the ongoing revision of annex I of Directive 2001/82/EC
    2. involve industry at an early stage in the development of the paper on minimum data requirements
    3. create a platform for industry and the EMEA to further discuss proposals for legislative and regulatory amendments on the subject
25. At the February CVMP meeting the Committee adopted a Reflection Paper (EMEA/CVMP/IWP/46853/2006)[10] about the minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use in birds against H5 and/or H7 highly pathogenic avian influenza virus for immediate publication.
    At the same meeting the CVMP adopted a guideline on the procedure for accelerated assessment pursuant to Article 39(8) of Regulation (EC) 726/2004 (EMEA/CVMP/32995/2006-rev.1) and agreed to publish the document for one month's public consultation. It is evident that this guideline will be of particular relevance to any forthcoming centralised avian influenza vaccine applications.
26. In the Reflection Paper the CVMP considers that the concept of a core-dossier approach similar to that developed for human pandemic influenza vaccines should be adapted and applied to avian influenza vaccines for veterinary use in emergency situations.
27. The European Commission's agreement would be required to amend the legislation to implement these concepts and further guidance would be required from CVMP to specify the requirements to be met. Additionally, the rapid inclusion of new strains for an authorisation in the event of incursion of a new antigenic variant into the EU and release of this vaccine as an authorised product is required. Therefore, the European Commission's approval is sought for amendments to the legislation, which allow such concepts as the veterinary legislation is currently more prescriptive than that on the human side.
28. To date the EMEA has received two letters of intent to submit applications for centralised authorisations for avian influenza vaccines for birds with proposed submission dates in April 2006. In total EMEA has been notified of five companies that may be interested in submitting applications.

[10] http://www.emea.eu.int/pdfs/vet/iwp/4685306en.pdf

29. On the 7th March, in response to a request from IFAH Europe, the Executive Director of the EMEA signed a fee waiver in respect of the notifications received to date for submission of applications for avian influenza vaccines for birds.
30. On the 8th March, the EMEA hosted a Platform on measures to promote availability of avian influenza vaccines for birds[11] involving the EMEA, DG's SANCO and Enterprise of the European Commission, national experts and members of the CVMP, and industry. Agreement was reached on the practical measures that could be taken by all sides to accelerate the availability of centrally authorised vaccines.
31. At the March meeting of the CVMP, the letters of intent were accepted and there was agreement in principle that the Reflections Paper on data requirements should be converted into a full guideline on authorisation of avian influenza vaccines, following formal adoption of a Concept Paper outlining the approach and scope.

This briefing note records the progress made by the EMEA in its preparation for an Influenza Pandemic, its collaboration with European Commission Directorates-General, involved agencies and with WHO, and its support to pharmaceutical industry developing pandemic influenza vaccines for human and veterinary use.

[11] http://www.emea.eu.int/pdfs/general/direct/pr/8605606en.pdf