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Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON REQUIREMENTS FOR VACCINES FOR USE IN BIRDS AGAINST AVIAN INFLUENZA VIRUS

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1. INTRODUCTION

During the autumn of 2005 the CVMP began to consider initiatives in relation to avian influenza at the request of the European Commission. The main factors leading to these discussions were the growing threat of outbreaks of avian influenza in bird populations within the European Union and the lack of vaccines with Marketing Authorisations within the Community.

In the case of a lack of suitably authorised products for birds National Competent Authorities can respond to an outbreak of avian influenza with emergency vaccination by implementing Article 8 of Directive 2001/82 /EC as amended by Directive 2004/28/EC to provisionally allow the use of vaccines without an authorisation. However, there is an unequivocal preference by all stakeholders, notably National Competent Authorities, farmers and consumers, to have access to vaccines with a Marketing Authorisation that is valid for the territory concerned for Member States to use.

The CVMP strongly supports the advantages of avian influenza vaccines being submitted via the centralised procedure to achieve a harmonised pan-European approach to such vaccines and to ensure that authorised vaccines are equally available in all Member States.

The CVMP, therefore, adopted on 16 February 2006 a reflection paper on 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 to provide stakeholders with an early opportunity to provide comments on their initiatives.

At a meeting with avian influenza vaccines manufacturers, European experts and the European Commission on 8 March 2006, detailed discussions on the reflection paper led to a unanimous conclusion that the reflection paper should be developed into a full guideline as a priority activity.

The Committee is consequently publishing this concept paper on a guideline on requirements for vaccines for use in birds against avian influenza virus. The scope of the guideline is more extensive than that of the reflection paper in order to give more comprehensive guidance in relation to avian influenza vaccines and to ensure that the guideline is relevant not only to the emergency situation at the time of its development (early 2006) but also to a range of foreseeable future epidemiological situations (sporadic, epizootic or endemic disease situations with and without the use of vaccination as a method of control). Comments are invited by the end of May 2006.

The extent to which the approach proposed in this concept paper can be covered by the existing legislation and the extent to which legislation will need to be amended to meet the technical requirements aare currently under consideration by the legal services of the EMEA and the European Commission.

2. PROBLEM STATEMENT

The current regulatory framework acts as a disincentive to manufacturers of veterinary vaccines for use against diseases with a highly variable antigenic nature (in particular avian influenza, foot-and-mouth disease and bluetongue) to seek authorisation of their vaccines within the EU. Competent Authorities are able to use such vaccines under the Article 8 ‘emergency provisions’ of Directive 2001/82/EC as amended without the need for an authorisation and manufacturers are aware that they will do so in the event of a disease emergency. Similarly, once a national authorisation has been granted by one Member State, Article 7 permits its authorisation by other Member States ‘where the health situation so requires’, thereby removing the incentive for the marketing authorisation holder to seek mutual recognition of the initial authorisation. The almost total lack of authorised products for such diseases, coupled with their repeated use in emergency situations in recent years, both point to the need for regulatory measures to promote their authorisation. These measures need to provide manufacturers with the flexibility to formulate vaccines using the most appropriate strains to meet a

particular epidemiological situation and to be able to rapidly introduce new strains as the situation changes, all whilst ensuring that appropriate standards of quality, safety and efficacy are maintained. Special measures exist for rapid introduction of new strains into vaccines against human influenza in man. However, it must be recognised that the epidemiology of the disease and the need for disease control programmes is sufficiently different for avian influenza when compared to human influenza that there is need to develop 'veterinary specific' measures. In the case of avian influenza, there is a real need for vaccines containing more than one avian influenza strain. Past experience with the disease in Italy and in countries outside the European Union proves that an "old" strain might well continue to stay relevant or even return to be the most relevant strain in the future, providing sufficient argumentation to keep this strain in the authorisation. The need for DIVA (**d**ifferentiation of **i**nfection from **va**ccination) control strategies also supports the inclusion of more than one strain into an authorisation. Additionally, there does not currently exist a well-defined procedure to provide globally approved reference strains for inclusion into all relevant marketing authorisations by a World Reference Laboratory, as is the case for human influenza. This places more emphasis on the ability of manufacturers to be able to rapidly provide and include a strain into an existing authorisation. As there are neither plans nor funds to give this role to the existing network of veterinary influenza laboratories in the foreseeable future, it is prudent of manufacturers to aim for a more flexible approach in order to meet the demands of Member States for suitable vaccines within appropriate timeframes.

Currently, substitution of one strain of an organism in a vaccine with another strain of the same organism requires either a line extension, as described in Annex II to the variation regulations (EC) 1084/2003 and 1085/2003, or a completely new authorisation. The addition of a strain to a vaccine always requires a new authorisation. These procedures do not therefore permit the rapid addition or substitution of an influenza vaccine strain in the event of incursion of a new antigenic strain into the EU. This procedure could be considerably shortened by amendments to the variation regulations to apply to animal influenza vaccines similar, but more flexible, provisions to those described in Articles 7 and 8 of these regulations for human influenza vaccines for routine and pandemic situations, respectively. The final paragraph of Article 8 permits a similar, rapid procedure for approving variations to be applied to other human pandemic situations and the same provision on the veterinary side would permit application of the approaches and procedures developed for animal influenza vaccines to be applied to other epizootic diseases of animals such as FMD and Bluetongue.

In many ways the approach proposed is similar to that accepted for allergens in the Guideline on Specific Requirements for the Production and Control of Allergen Products in Volume 7 of The Rules Governing Medicinal Products in the European Union (http://pharmacos.eudra.org/F2/eudralex/vol-7/B/7Blm11a.pdf). In this context, it is stated that

'In certain required testing programmes data obtained with one representative allergen product may be extrapolated to another. However, this is only acceptable if a close relationship exists between their active components, particularly with respect to the properties being examined'.

The guideline on avian influenza vaccines will likewise be based on the principle that many of properties of inactivated avian influenza antigens although derived from different seed strains, may be assumed to be the same in terms of quality, safety and efficacy, provided that they are produced to GMP using a standard method of manufacture.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The CVMP considers that the concept of an "umbrella dossier" containing a pool of authorised Master Seeds from which the manufacturer can then select a number of antigens, up to a specified limit, to formulate each batch of product should be applied. This concept has been considered within the Position Paper on requirements for Vaccines against Foot-and-Mouth Disease (FMD) (EMEA/CVMP/775/02) and has already led to national authorisations for this disease in a number of Member States.

It is important to differentiate between the core-dossier and mock-up vaccine concepts as currently used on the human side to authorise pandemic influenza vaccines and contrast this to the umbrella

dossier approach that will be developed within the guideline. The umbrella concept is novel insofar as it proposes that a limited number of defined antigens are included within the authorisation for an avian influenza vaccine for use in birds, based on data provided in the application on the quality, safety and efficacy of these antigens. The authorisation also defines the maximum number and amount of these antigens that can be blended to produce the final product, based on the safety and efficacy data presented in the dossier. Thus the dossier and the SPC are specific about the antigens included within the authorisation and about the number and amount of antigens that can be included in any blend of released produced, but are not specific about the precise antigens contained within each batch. This information would be provided as part of the batch release documentation, product labelling and packaging information supplied with each batch. In several aspects therefore, the approach foresees the different, defined combinations of antigens as different presentations of the same medicinal product covered by a single authorisation.

This "umbrella dossier" concept is therefore different from the approach for human pandemic vaccines where the manufacturer provides a mock-up dossier based on one strain and in the case of a pandemic then changes the strain via a variation procedure rather than requiring a new authorisation. The umbrella dossier approach takes this concept further in that variations would not be required for each vaccine composition that is marketed, provided the antigens used are included within the authorisation. Furthermore, to make the umbrella concept fully effective for avian influenza vaccines it would be necessary to revise the variation regulations along the lines of the approach for human influenza vaccines to allow for the addition and/or substitution of new strains onto an authorisation in the event of an incursion of a new antigenic strain into the EU via an abbreviated variation procedure, as described in Section 3, above. As with other vaccines, changes to the **amount** of each antigen included in a vaccine would be subject to a type II variation procedure whereas changes to increase the **number** of different antigens that could be incorporated into a vaccine would require a new authorisation (i.e. a bivalent vaccine could not be changed to a trivalent vaccine, the trivalent vaccine would require a new authorisation). The issue of whether or not a vaccine could be blended with a reduced number of antigens will need to be considered during preparation of the guideline (i.e. if quality, safety and efficacy data have been approved for a bivalent vaccine would this also enable formulation as a monovalent vaccine and, if so, with what restrictions).

Article 12(3) of Directive 2001/82/EC, as amended by Directive 2004/28/EC lists the administrative, safety, quality and efficacy data that shall be presented in support of the application. In particular, Article 12(3)(c) establishes that the application shall include the qualitative and quantitative composition of all the constituents of the medicinal product. The umbrella dossier approach complies with the requirements set out in this provision, as the authorisation would be explicit in terms of the quantitative and qualitative composition of the product. In this respect the authorisation would specify the amount and nature of all the ingredients including excipients, adjuvants and active ingredients in terms of the amount of inactivated avian influenza antigens that would be included per dose of vaccine to be administered. What would not be fixed as part of the authorisation would be the seed strain of origin of the avian influenza antigens, as these would be selected according to need from the list approved within the authorisation. The umbrella approach therefore relies in essence on defining the 'quantitative and qualitative composition' of the active ingredients of the medicinal product as specified amounts of a limited number of approved, inactivated avian influenza antigens which have been included on the authorisation based on the submission of appropriate data and a justification for their epidemiological relevance for use within the EU.

4. RECOMMENDATION

The Committee recommends that a guideline should be prepared on requirements for vaccines for use in birds against avian influenza virus. This guideline should provide guidance to manufacturers on

- the minimum data requirements for authorisation of avian influenza vaccines for emergency use under Article 26 of Directive 2001/82/EC, as amended, and Article 39(7) of Regulation 726/2004 (the 'exceptional circumstances' clauses)

- the additional requirements that would need to be met in terms of specific obligations and follow up measures before the authorisation could be considered to contain a 'full dossier' meeting the requirements of the Annex to Directive 2001/82/EC as amended
- an explanation of the concept of the 'umbrella' dossier in terms of the requirements for inclusion of antigens onto the initial authorisation, the extent to which manufacturers may vary the vaccine in terms of number, amount and nature of antigens (all components other than antigen will be fixed for a given authorisation) and the requirements in terms of SPC, labelling, batch release etc to reflect the particular formulation of each batch of vaccine
- a proposal as to how the variations regulations (1084&1085/2003) should be amended to permit the rapid substitution and/or addition of new strains of avian influenza onto an existing authorisation
- the requirements for establishment and maintenance of 'antigen banks' for AI vaccine antigens and the applicability of the umbrella dossier and vaccine antigen master file approaches to such banks

Further details about the scope and contents of parts of the proposed guideline can be gained from the reflection paper on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against H5 and/or H7 highly pathogenic avian influenza viruses.

5. PROPOSED TIMETABLE

Initial consideration by CVMP on 15 March 2006 with a view to adoption of the concept paper at the April meeting. Formal release for consultation at April CVMP with a one month deadline for comments.
Discussion in IWP in June 2006, discussion in CVMP in June 2006, proposed date for release of draft guideline 21 June 2006, deadline for comments 30 September 2006, rediscussion in IWP in October 2006 and in CVMP in October 2006, expected dated for adoption by Committee in October 2006.
Due to the urgent need for guidance for all stakeholders this guideline will come into operation immediately following its adoption.

6. RESOURCE REQUIREMENTS FOR PREPARATION

1 Rapporteur, 1 drafting group meeting with ~ 8 experts in June 2006, 3 IWP meetings, 3 CVMP meetings. The possibility for a meeting at the close of the consultation period should be maintained, dependent on the responses received and the budget available.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline is anticipated to improve the availability of authorised avian influenza vaccines in the European Union, thereby greatly aiding all measures, which may become necessary for the control of the disease as outlined in Directive 2005/94/EC on control of avian influenza. The guideline is also expected to lead to a harmonised pan-European approach to the quality, safety and efficacy of avian influenza vaccines and provide Member States with clear and verifiable information on the risks and benefits of these vaccines. The industry will benefit from such a guideline as it will provide a clear standard for the dossier requirements for potential applications and will ensure a harmonised approach to the assessment of their respective avian influenza vaccine dossiers.

The guideline will serve as a model for other, similar diseases making amendment or development of guidelines for FMD and Bluetongue easier.

Development of the guideline will assist in the final revision of Annex 1 to Directive 2001/82/EC, as amended.

The guideline should increase regulatory certainty and thereby reduce the costs to industry of obtaining and maintaining authorisations for avian influenza vaccines.

8. INTERESTED PARTIES

European Commission, EU Member States, IFAH-Europe

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Reflection paper on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against H5 and/or H7 highly pathogenic avian influenza viruses (EMEA/CVMP/IWP/46853/2006).

Position paper on requirements for vaccines against Foot-and-Mouth Disease (FMD) (EMEA/CVMP/775/02).

Harmonisation of requirements for equine influenza vaccines specific requirements for substitution of the strain of an equine influenza vaccine (EMEA/CVMP/116/96)

Guideline on Specific Requirements for the Production and Control of Allergen Products in Volume 7 of The Rules Governing Medicinal Products in the European Union (http://pharmacos.eudra.org/F2/eudralex/vol-7/B/7Blm11a.pdf).