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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE**

**(CVMP)**

# REFLECTION PAPER: 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

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This paper does not open formal consultation but comments are welcome.
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## BACKGROUND INFORMATION

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 within the European Union and the lack of vaccines with Marketing Authorisations within the Community.

While 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 and provisionally allow the use of vaccines without an authorisation, there is an unequivocal preference to have access to vaccines with a Marketing Authorisation.

The CVMP, therefore, agreed short, medium and long-term actions with the objective of achieving Marketing Authorisations for avian influenza vaccines, which permit timely adaptations to pandemic situations.

In the short-term the Committee aims to provide a guideline 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. This harmonised data set can also be used by National Competent Authorities to authorise vaccines they might wish to use if emergency vaccination is applied.

The CVMP strongly supports the advantages of avian influenza vaccines being submitted via the centralised procedure in the interests of achieving a harmonised pan-European approach to such vaccines.

The CVMP is, therefore, publishing this reflection paper on such minimum data requirements in order to provide information on the current state of discussions on this topic which should form the basis of further drafting regarding the planned guideline.

In the medium term the CVMP proposes having legislative amendments in place, which would allow the authorisation of vaccines against avian influenza, and possibly even other diseases such as Foot-and-Mouth Disease (FMD), in order to permit authorised vaccines that can be adapted quickly to a pandemic situation.

The CVMP also recommends the implementation of incentives for the industry, similar to those that exist for human pandemic influenza vaccine applications, such as fee waivers and accelerated evaluation of applications for scientific advice and marketing authorisations. In this context the current development of a veterinary guideline on an accelerated assessment procedure for veterinary medicinal products (adopted for consultation at the February CVMP meeting EMEA/CVMP/32995/2006-CONSULTATION) is recognised by the Committee to be another step to facilitate authorisation of avian influenza vaccines in as short a time frame as possible, while still ensuring a scientifically sound and thorough assessment. Future discussions will look into possibilities to further shorten the time for assessment if necessary.

The CVMP considers that the concept of a core-dossier containing a large 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 could also be relevant for a number of vaccines designed to protect against disease caused by viruses, which have the potential for rapid mutation.

One of the most important requirements for useful guidelines for avian influenza vaccines would be to permit the 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. Provided that the European Commission agrees to legislative changes which allow such concepts, further guidance could then be provided which would propose requirements that must be met for 'full' acceptance of a master seed virus and antigen onto the authorisation and the requirements that should be deemed sufficient for release of vaccine formulated from a new master seed virus in the event of an emergency. It is of paramount importance that manufacturers are able to rapidly create and use new master seed viruses if any guidance for avian influenza vaccine is to be of value in the face of a serious disease epidemic. Data requirements for master seed testing would be addressed in scientific guidance and it may be possible to reduce testing if a "core" dossier demonstrates the ability of the inactivation procedure to inactivate likely contaminants.

In the long term the CVMP recommends a revision of the current regulatory approach to tests that allow differentiation of vaccination from infection.

Current pharmaceutical legislation does not cover the assessment and authorisation of diagnostic tests, even when such tests are an essential component of the use of a 'marker' vaccine in a DIVA (differentiation of vaccination from infection) vaccination campaign. Consideration should be given to including within the scope of the assessment procedure companion diagnostic tests to permit inclusion on the authorisation of a claim for reliable identification of infection in vaccinated animals.

## 1. LEGAL BASIS, SCOPE AND INTRODUCTORY REMARKS

For an authorisation under exceptional circumstances Article 39(7) of Regulation (EC) 726/2004 and Article 26(3) of Directive 2001/82/EC as amended by Directive 2004/28/EC apply. In addition to these provisions, this reflection paper has to be read in conjunction with the introduction and general principles and Title II of the Annex I to Directive 2001/82/EC as amended.

The scope of this document is restricted to vaccines intended for emergency use in birds.
For vaccines intended for routine preventive use the full requirements of Annex I Title II of Directive 2001/82 EC as amended apply.

Since this document is dealing with minimum data requirements for emergency vaccines only the SPC needs to reflect the specific areas where incomplete data have been provided.

For an avian species to be included in the section "Target Species" of the SPC the outlined safety and efficacy data have to be provided. In the case that only incomplete but relevant safety and efficacy data for a given species is available this will be stated elsewhere in the SPC.

The vaccine must only contain one or more suitable avian influenza virus strains.

The vaccine must be manufactured under GMP conditions.

The use of conventional live vaccines is not acceptable.

## 2. ANALYTICAL PART

The dossier should provide at least the following information:

- The qualitative and quantitative composition of the vaccine including the excipients and the adjuvants. The active ingredient can be a live recombinant or an inactivated antigen (conventional inactivated viruses or obtained by reverse genetics systems). The origin of the vaccine strains is not relevant as long as they can induce protection against the epidemiologically relevant H5 and/or H7 highly pathogenic avian influenza virus strains.

- The virus strain(s) used to produce conventional inactivated vaccines should preferably be of low pathogenicity.

- A description of the manufacturing method. A quantification of the antigen content is compulsory (titre for live vaccines or antigen content after inactivation for inactivated vaccines).

- For the inactivated vaccines, the validation of the inactivation should be provided. To test for complete inactivation two passages in eggs will probably be sufficient. If the applicant company has experience with inactivation of other influenza strains, the evidence of which should be provided, demonstration of complete inactivation at 67% of the total time allowed will be sufficient. Otherwise a full set of data with intermediate values will be necessary.

- The tests and results to demonstrate freedom from extraneous agents, which are carried out (bacteria, fungi, viruses, mycoplasma) on each starting material of biological origin.

- The source of eggs used for the preparation of inactivated vaccines, together with information on the controls applied to minimise the risks of extraneous agents. For inactivated vaccines produced in eggs from healthy flocks it would be helpful if, coupled with this information on starting materials, information could be provided on the ability of the inactivation process

applied to the antigen also to inactivate extraneous agents. If this cannot be applied then only SPF eggs should be used for the production.

- The control of the finished product including a description of the safety and titre or potency tests (correlated with the antigen content) performed on the finished product in SPF chickens, the limits of acceptance and a declaration of the applicant that certifies that the results are within the specifications.

- The usual requirements for stability should be put in place as soon as possible for the vaccine. In the meantime supporting data of the experience with other influenza vaccines for veterinary use would be acceptable with a maximally granted shelf-life of 12 months.

- If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18 EC as amended, the full set of data with regard to Directive 2001/18 EC should be provided. It is however acceptable to fulfil part of the requirements through data which has been gained with similar GMO constructs already authorised.

- If the vaccine contains an inactivated medicinal product as defined under the Annex of Regulation (EC) No 726/2004 no additional data are required.

## 3. SAFETY PART

The safety of the administration of an overdose to birds of the minimum age recommended for vaccination should be demonstrated in laboratory studies for all recommended target species (e.g. chickens, ducks and turkeys). For inactivated vaccines, if data are available with other vaccines of similar composition (excipients and adjuvants) in the same or a similar range of target species these could be used to fulfil the requirements. The availability of safety data for repeated administration and in other avian species would be helpful. Lack of data on repeated administration may lead to a specific obligation to be fulfilled at a later date.

Concerning safety in laying birds, whenever data related to other vaccines of similar composition are available these data could be used to fulfil the requirements with regard to reproductive performances.

If the vaccine contains a GMO according to Directive 2001/18/EC, all the requirements of Part 7 Section C Chapter 6 of Directive 2001/82/EC should be fulfilled.

If the vaccine contains an inactivated medicinal product as defined under the Annex of Regulation (EC) No 726/2004 no additional data are required.

All available data on safety in other species should be provided.

No field trials are required.

## 4. EFFICACY PART

The efficacy should be demonstrated in laboratory conditions by a challenge model aimed to define the onset and the duration of immunity. The challenge should be relevant to the current disease risk situation in the EU.

The major goal is the demonstration of a significant reduction of excretion and transmission of the challenge virus. The vaccination should provide a significant reduction or suppression of viral excretion and transmission at oro-nasal and cloacal levels from vaccinated animals. The level of

reduction of excretion and transmission of the challenge virus will be mentioned for each target species in the SPC. A significant reduction of clinical signs is also expected.

**Onset of immunity**

Any claim to be made for the onset of immunity will depend on the results of the studies performed by the Applicant. It is expected that the onset of immunity should be as rapid as possible to allow the use of the vaccine in emergency conditions

**Duration of immunity**

Any claim to be made for the duration of immunity should be demonstrated, and will depend on the results of the studies performed by the applicant. It is expected that the immunity induced by the vaccine should cover the economic life of the target species. Any need for revaccination should be justified and all relevant data should be provided.

If data on vaccination in the face of infection is available this should be provided in order to be reflected in the SPC if relevant.

All available data on efficacy for species other than the target species with special attention to ducks and turkeys should be provided.

No field trials are required.