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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 AGAINST BLUETONGUE

AGREED BY THE DRAFTING GROUP ON BLUETONGUE VACCINES BY THE IMMUNOLOGICALS WORKING PARTY	7 March 2007
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This paper does not open formal consultation but comments are welcome.
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BACKGROUND INFORMATION

This reflection paper has been developed in response to the growing threat of outbreaks of Bluetongue within the European Union and the lack of vaccines with marketing authorisations within the Community.

Bluetongue (BT) is a non-contagious, insect-transmitted disease of certain species of domestic and wild ruminants that is caused by BT virus (BTV). BTV infection of ruminants occurs throughout temperate and tropical regions of the world, coincident with the distribution of specific species of *Culicoides* biting midges that are biological vectors of the virus.
To date, 24 distinct serotypes of BT virus have been described that all share common group antigens but which are distinguished on the basis of serotype-specific virus neutralization assays. The genetic variation amongst strains of BTV results in differences in the pathogenesis and expression of disease in BTV- infected ruminants, and in the sensitivity and specificity of diagnostic tests and the vectorial competency of culicoides populations.

Bluetongue is principally a disease of sheep and other domestic and wild ruminant species. Cattle and goats are usually sub-clinically infected, thus the occurrence of severe BT amongst cattle during the ongoing epidemic in northern Europe is notable.
BT has a big economic impact on the sheep, goats and cattle industry for the following reasons:

- direct losses in sheep, goats and cattle dependent on the virulence of the strain, host's susceptibility and environmental factors,
- application of animal movement restrictions leading to an almost complete ban on the movement of ruminant species from infected to free zones.

While in the case of a lack of suitably authorised products National Competent Authorities can respond to an outbreak of Bluetongue 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 use of unauthorised vaccines could potentially have negative effects in the field (especially for live vaccines, introduction of exotic extraneous agents or reversion to virulence).

The CVMP, therefore, agreed actions with the objective of achieving Marketing Authorisations for Bluetongue vaccines.

The Committee aims to provide a guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against Bluetongue. 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 Bluetongue 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.

Similar to its recommendations for avian influenza vaccines the CVMP again proposes having legislative amendments in place, which would allow the authorisation of vaccines against avian influenza, Foot-and-Mouth Disease (FMD) and Bluetongue, in order to permit authorised vaccines that can be adapted quickly to the incursion of a new strain.

The CVMP considers that the concept of a multistrain dossier as currently proposed in the draft proposal for a revision for Annex I of Directive 2001/82/EC should also apply to Bluetongue vaccines. A multistrain dossier contains 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.

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.

In consideration of the urgent need to make authorised products available, the CVMP decided that it is appropriate to make use of the provisions of Article 26 of Directive 2001/82/EC, as amended, and Article 39(7) of Regulation 726/2004 (the exceptional circumstances clauses) to facilitate rapid authorisation of vaccines in advance of generation of data to meet the full requirements of Annex I to Directive 2001/82/EC as amended.

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 inactivated and live recombinant vaccines intended for emergency use against Bluetongue.

For live conventional vaccines and vaccines intended for routine preventive use the full requirements of Annex I Title II of Directive 2001/82 EC as amended apply. This reflection paper is not applicable to conventional live vaccines due to the risk amongst others of viraemia, transmission of the vaccine virus and recombination of strains.

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 a 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 Bluetongue virus serotypes or antigens relevant to the epidemiological situation.

The vaccine must be manufactured under GMP conditions.

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.
- A description of the manufacturing method. A quantification of the antigen content is compulsory. In principle, this should be the antigen content after inactivation for inactivated vaccines and the titre for live recombinant vaccines. If an appropriate antigen quantification is not available, the virus titre before inactivation may be considered as long as a correlation with vaccine efficacy can be demonstrated.
- For inactivated vaccines, validation of the inactivation process should be provided.
- 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 description of the production and the control of the active ingredient(s) shall be complete and the corresponding results have to be provided.
- The TSE risk must be evaluated and the product must be in compliance with the CVMP TSE NfG. The control of the finished product including a description of the safety and potency tests (titre or correlated with the antigen content for inactivated vaccines) performed on the finished product, the limits of acceptance and a declaration of the applicant which certifies that results are within the specifications. The control of inactivation can be done on the final bulk.
- The usual requirements for stability should be put in place as soon as possible for the vaccine. In the mean time and in the absence of data a maximum shelf-life of 12 months may be granted.
- 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 2001/82/EC should be provided. It is however possible to fulfil part of the requirements through data which have been gained with similar GMO constructs already authorised. As for inactivated vaccines, a maximum shelf-life of 12 months may be granted in the absence of stability data.

3. SAFETY PART

For all the vaccines (inactivated and live recombinant vaccines), the following data are requested:

The safety of the administration of an overdose of vaccine should be demonstrated in laboratory studies for all the target species of the minimum age recommended for vaccination.. Safety data for repeated administration should be provided if repeated administration is recommended in the vaccination schedule.

If the use in pregnant animals is indicated in the product literature the examination of reproductive performance should be carried out.

All available safety data in other non-target ruminant species should be provided.

Any field data should be provided, but specific trials are not required.

For inactivated vaccines representative experimental batches or standard production batches can be used. For these 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

If the vaccine contains a GMO according to Directive 2001/18/EC, all the requirements of Part 7 section C Chapter 4, 5 and 6 of Directive 2001/82/EC should be fulfilled.

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4. EFFICACY PART

The efficacy of the vaccine should be demonstrated in laboratory conditions by a challenge model aimed to define the onset and duration of immunity for each of the indicated target species. The challenge virus should be relevant to the current epidemiological situation in the EU. For inactivated vaccines representative experimental batches or standard production batches can be used.

The main parameter of efficacy of the vaccine is a substantial reduction in viraemia post-challenge. If it is not possible to achieve this goal the acceptable level of efficacy will be established on a case by case basis taking into account for example prevention or reduction of clinical signs.

The methods used to detect the post-challenge viraemia should be validated. The combination of methods such as virus isolation and RT-PCR would normally allow the best follow up.

Any field data should be provided, but specific trials are not required
The onset of immunity should be as rapid as possible to allow the use of the vaccine in emergency conditions. Any claim to be made for the onset of immunity will depend on the results of the studies performed by the Applicant. As a minimum, challenge at one time point after vaccination is required. The onset of immunity will allow to define when the animals are protected.
The vaccination schedule (one or two doses for the primary vaccination) should be justified.

It is expected that the duration of immunity induced by the vaccination should cover the risk period. 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. Serology will be accepted if it is demonstrated that the level of titre measured is correlated with protection. Any need of revaccination should be justified and the effectiveness of the vaccination should be demonstrated.

BT vaccines which would allow the differentiation between infected and vaccinated animals would be desirable. The applicant will have to provide data to substantiate this property.