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**GUIDELINE ON REQUIREMENTS FOR AN AUTHORISATION UNDER EXCEPTIONAL
CIRCUMSTANCES FOR VACCINES FOR EMERGENCY USE AGAINST BLUETONGUE**

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TABLE OF CONTENTS

| | | |
|----|--|---|
| 1. | INTRODUCTION (BACKGROUND) | 3 |
| 2. | SCOPE..... | 4 |
| 3. | LEGAL BASIS..... | 4 |
| 4. | MINIMUM DATA REQUIREMENTS FOR AN AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES FOR VACCINES FOR EMERGENCY USE AGAINST BLUETONGUE | 5 |

1. INTRODUCTION (BACKGROUND)

This guideline has been developed in response to the growing threat of outbreaks of Bluetongue within the northern part of Europe 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.

Bluetongue 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, Member states 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 authorised vaccines. In consideration of the urgent need to make suitable authorised products available, 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. Vaccination against BTV is a very important tool for the control of the disease and is also used to permit 'safe' trade in live ruminants in accordance to OIE standards and EU legislation. In considering the requirements for the Bluetongue vaccines it is necessary to take account of the various scenarios in which they may be used:

Emergency vaccination, i.e. targeted use to directly combat an outbreak in an EU member state or in case of a perceived immediate threat of infection occurring.

Preventive vaccination, i.e. longer term vaccination to try to reduce the risk of the disease spreading into populations considered to be at risk.

Routine vaccination, i.e. to maintain a high degree of immunity irrespective of the perceived risk of infection.

As 24 serotypes of BT virus have been identified, there may be a need to respond quickly to a rapid evolving epidemiological situation to make vaccines available to combat the specific serotype circulating in the field. This may result in an urgent need to produce new vaccines using serotypes not previously authorised or to change the serotypes used in authorised vaccines at short notice.

There is often a need for vaccines containing more than one bluetongue serotype. Past experience with the disease through Europe shows that an "old" serotype might well continue to stay relevant or even return to be the most relevant serotype in the future, demonstrating that the regulatory framework needs to be adapted to facilitate maintaining this serotype in the authorisation, but also having the flexibility to include new serotypes that are epidemiologically relevant.

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 bluetongue, avian influenza and foot-and-mouth disease) to seek authorisation of their vaccines within the EU. 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 serotypes to meet a particular epidemiological situation and to be able to rapidly introduce new serotypes as the situation changes, while ensuring that appropriate standards of quality, safety and efficacy are maintained.

This guideline aims to provide guidance to applicants on the minimum data requirements for authorisation of bluetongue vaccines for emergency use under Article 26 of Directive 2001/82/EC, as amended, and Article 39(7) of Regulation 726/2004. Additional guidance on measures to facilitate the rapid inclusion of new or different virus serotypes in authorised vaccines and advice on requirements for vaccines intended for use in particular epidemiological situations will be the subject of a future revision.

2. SCOPE

The scope of this document is restricted to applications for an authorisation under exceptional circumstances according to Article 39(7) of Regulation (EC) 726/2004 for vaccines against bluetongue virus infections.

The full requirements of Annex I to Directive 2001/82/EC apply for live conventional vaccines and vaccines intended for routine and preventive vaccination.

Guidance on vaccines for use with a DIVA (differentiation of infection from vaccination) strategy, changing or adding new serotypes of bluetongue virus to an authorised vaccine and requirements for vaccine banks will be included in a future revision of this guideline.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and Title II of the Annex I to Directive 2001/82/EC as amended.

The introduction, general principles and Title II of the Annex I to Directive 2001/82/EC as amended, list the administrative, quality, safety and efficacy data that should be presented in support of an application.

Article 39(7) of Regulation (EC) 726/2004 and Article 26(3) of Directive 2001/82/EC as amended by Directive 2004/28/EC make provision for an authorisation under exceptional circumstances where it is anticipated that additional studies may be required to meet the full requirements of Annex I Title II of Directive 2001/82/EC as amended.

It should also be noted that the use of vaccines against bluetongue within the EU is controlled under other EU legislation, notably Directive 2000/75/EC.

4. MINIMUM DATA REQUIREMENTS FOR AN AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES FOR VACCINES FOR EMERGENCY USE AGAINST BLUETONGUE

It is anticipated that, in the event of a vaccine being required to combat an outbreak of bluetongue, all of the tests required to meet full requirements of Annex I Title II of Directive 2011/EC may not have been completed. The following sections outline the minimum requirements that should be met for a Marketing Authorisation to be issued in accordance with Article 39(7) of Regulation (EC) 726/2004 and Article 26(3) of Directive 2001/82/EC.

4.1 General requirements

If data meeting the full requirements of Annex I Title II of Directive 2001/82/EC are not available, the SPC should reflect any specific areas (e.g. maternally derived antibodies impact) 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. If only incomplete but relevant safety and efficacy data are available for a given species this will be stated elsewhere in the SPC.

The vaccine must only contain suitable bluetongue virus serotypes (one or more).

The vaccine must be manufactured under GMP conditions.

No expert reports are requested.

A thorough benefit/risk assessment regarding both vaccination and the disease situation has to be provided.

4.2 Analytical (Quality) requirements

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. The formulation should ensure a minimum antigen content in relation with the antigen content demonstrated to be efficacious in the efficacy studies. A quantification of the antigen content is compulsory. In principle, this should be the antigen content after inactivation for inactivated vaccines. However, 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. As indicated in the Ph. Eur 5.2.5. if during the manufacturing process, the applicant applies a treatment considered to be able to reduce or eliminate extraneous agents, he has to provide the validation of its inactivating capacity. The testing of extraneous agents can be reduced if the applicant can provide a valid risk assessment and a valid risk management that show the absence of risk related to the use of starting materials 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 because part of the raw materials are of ruminant origin and the finished product is intended for ruminants.

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, 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 and in the absence of data, a maximum shelf-life of 12 months may be granted.

The use of stability data of a BTV vaccine containing other serotypes but having the same composition in adjuvants and excipients may be used to define the shelf life.

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.

4.3 Safety requirements

The safety of the administration of one dose of the vaccine should be demonstrated in laboratory studies for all recommended target species of the minimum age recommended for vaccination. 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 safety data for repeated administration should be provided if repeated administration is recommended in the vaccination schedule. The repeat dose test can be combined with the one dose test.

For inactivated vaccines representative experimental batches can be used. The use of standard production batches is possible if the vaccine contains a fixed antigenic amount that is controlled at the formulation step.

Due to the expected large use of this type of vaccine, the examination of reproductive and lactating performances after vaccination should be carried out. Whenever data related to other vaccines of similar composition (excipients and adjuvants) and similar vaccination schedule are available these data could be used to fulfil the requirements with regard to reproductive performance.

The absence of data is acceptable when the dossier is submitted for the first time but the applicant has to provide a commitment to perform the appropriate studies in a reasonable timeframe. In this case, the SPC will clearly indicate the absence of data.

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.

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

No field trials are required. Data on previous use in the field should be provided if available.

4.4 Efficacy requirements

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 category of the indicated target species. If data are missing for some categories of the indicated target species, the SPC will reflect this.

The challenge virus should be relevant to the current epidemiological situation in the E.U.

For inactivated vaccines representative experimental batches can be used. The use of standard production batches is possible if the vaccine contains a fixed antigenic amount that is controlled at the formulation step.

The main parameter of efficacy of the vaccine is a prevention in viraemia post-challenge accompanied by the absence of clinical signs (if relevant). If it is not possible to achieve this goal the acceptable level of efficacy will be established on a case by case basis using a risk/benefit approach taking into account for example available data on level of reduction of viraemia, reduction of clinical signs, prevention or reduction of transplacental infection.

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

No field trials are required.

Onset of immunity

The speed of onset of immunity should be fully taken into account in the risk/benefit assessment in order 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 using animals vaccinated at the minimum age recommended in the SPC at one time point after vaccination is required. The onset of immunity will allow to define when the animals are protected.

The efficacy of the vaccination schedule (one or two doses for the primary vaccination) should be demonstrated.

Duration of immunity

The absence of establishment of the duration of immunity is acceptable when the dossier is submitted for the first time but the applicant has to provide a commitment to perform the appropriate study in a reasonable timeframe. In this case, the SPC will clearly indicate the absence of data.

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. An alternative indicator of efficacy (e.g. serology) may be used to support a duration of protection if a correlation between the level of this indicator and protection has been demonstrated .

Any need of revaccination should be justified and all relevant data should be provided.

Marker vaccine

BT vaccines which would allow the differentiation between infected and vaccinated animals would be desirable to allow a DIVA vaccination campaign. For these 'marker' vaccines where the marker claim is reliant on in vitro diagnostic tests, sufficient data on the diagnostic tests shall be provided to allow adequate assessment of the claims related to the marker properties.