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Mannheimia Vaccine (Inactivated) for Sheep

General Notices

(Ph. Eur. monograph 1946)

Ph Eur

1 DEFINITION

Mannheimia vaccine (inactivated) for sheep is a preparation of one or more suitable strains of *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*), inactivated while maintaining adequate immunogenic properties. This monograph applies to vaccines intended for the active immunisation of sheep and/or for the passive protection of their progeny against disease caused by *M. haemolytica*.

2 PRODUCTION

2-1 PREPARATION OF THE VACCINE

Production of the vaccine is based on a seed-lot system. The seed material is cultured in a suitable medium; each strain is cultivated separately and identity is verified using a suitable method. During production, various parameters such as growth rate are monitored by suitable methods; the values are within the limits approved for the particular product. Purity and identity of the harvest are verified using suitable methods. After cultivation, the bacterial suspensions are collected separately and inactivated by a suitable method. The vaccine may be adjuvanted.

2-2 CHOICE OF VACCINE COMPOSITION

The choice of composition and the strains to be included in the vaccine are based on epidemiological data on the prevalence of the different serovars of *M. haemolytica* and on the claims being made for the product, for example active and/or passive protection.

The vaccine is shown to be satisfactory with respect to safety (*5.2.6*) and efficacy (*5.2.7*) for the sheep for which it is intended.

The following tests for safety (section 2-2-1) and immunogenicity (section 2-2-2) may be used during the demonstration of safety and efficacy.

2-2-1 Safety

2-2-1-1 Laboratory tests. Carry out the tests for each route and method of administration to be recommended for vaccination and in sheep of each category for which the vaccine is intended (for example, young sheep, pregnant ewes). Use a batch of vaccine containing not less than the maximum potency that may be expected in a batch of vaccine.

For each test, use not fewer than 8 sheep that preferably do not have antibodies against the serovars of *M. haemolytica* or against the leucotoxin present in the vaccine. Where justified, sheep with a known history of no previous mannheimia vaccination and with low antibody titres (measured in a sensitive test system such as ELISA) may be used. Administer to

each sheep 1 dose of the vaccine. If the schedule to be recommended requires a 2nd dose, administer another dose after an interval of at least 14 days. Observe the sheep at least daily for at least 14 days after the last administration. If the test is carried out in pregnant ewes, observe the ewes until 1 day after lambing. Record body temperature the day before vaccination, at vaccination, 2 h, 4 h and 6 h later and then daily for 4 days; note the maximum temperature increase for each sheep.

The vaccine complies with the test if:

— no sheep shows abnormal local reactions or notable signs of disease, or dies from causes attributable to the vaccine,

— the average body temperature increase for all sheep does not exceed 1.5 °C and no sheep shows a rise greater than 2.0 °C, and if

— no adverse effects on gestation or the offspring are noted if the test is carried out in pregnant ewes.

2-2-1-2 Field studies. The sheep used for the field trials are also used to evaluate safety. Carry out a test in each category of sheep for which the vaccine is intended. Use not fewer than 3 groups of 20 sheep with corresponding groups of not fewer than 10 controls in 3 different locations. Examine the injection sites for local reactions after vaccination. Record body temperatures the day before vaccination, at vaccination and on the 2 days following vaccination.

The vaccine complies with the test if no sheep shows abnormal local or systemic reactions or notable signs of disease, or dies from causes attributable to the vaccine. The average body temperature increase for all sheep does not exceed 1.5 °C and no sheep shows a rise greater than 2.0 °C. In addition, if the vaccine is intended for use in pregnant ewes, no adverse effects on the gestation or offspring are demonstrated.

2-2-2 Immunogenicity

2-2-2-1 Active immunisation. For vaccines with claims for active immunisation against mannheimiosis, carry out a test for each serovar of *M. haemolytica* for which protection is to be claimed on the label.

A test is carried out for each route and method of administration to be recommended, using in each case lambs of the minimum age to be recommended for vaccination. The vaccine administered to each lamb is of minimum potency.

Use not fewer than 20 lambs that do not have antibodies against *M. haemolytica* and against the leucotoxin of *M. haemolytica*. Vaccinate not fewer than 10 lambs according to the schedule to be recommended. Maintain not fewer than 10 lambs as controls. 20-22 days after the last vaccination, challenge each lamb by the intratracheal route or by another appropriate route, with a sufficient quantity of a low-passage, virulent strain of a serovar of *M. haemolytica*. Where necessary for a given serovar, prechallenge with parainfluenza type 3 (PI3) virus or another appropriate respiratory pathogen may be used. Observe the lambs for a further 7 days; to avoid unnecessary suffering, severely ill lambs are euthanised and are then considered to have died from the disease. During the observation period, examine the lambs for signs of disease (for example, increased body temperature, dullness, abnormal respiration) and record the mortality. Euthanise surviving lambs at the end of the observation period. Carry out post-mortem examination on any lamb that dies and those euthanised at the end of the observation period. Examine the lungs and evaluate the extent of lung lesions due to mannheimiosis. Collect samples of lung tissue for re-isolation of the challenge organisms. Score the clinical observations and lung lesions and compare the results obtained for these parameters and the bacterial re-isolation results for the 2 groups.

The test is not valid if signs of *M. haemolytica* infection occur in less than 70 per cent of the control lambs. The vaccine complies with the test if there is a significant difference between the scores obtained for the clinical and post-mortem observations in the vaccinates compared to the controls. For vaccines with a claim for a beneficial effect on the extent of infection against the serovar, the results for the infection rates are also significantly better for the vaccinates compared to the controls.

2-2-2-2 Passive protection. For vaccines with claims for passive protection against mannheimiosis carry out a test for each serovar of *M. haemolytica* for which protection is to be claimed on the label.

A test is carried out for each route and method of administration to be recommended for vaccination. The vaccine administered to each ewe is of minimum potency.

Use not fewer than 6 ewes that preferably do not have antibodies against the serovars of *M. haemolytica* or against the leucotoxin present in the vaccine. Where justified, ewes with a known history of no previous mannheimia vaccination, from a source with a low incidence of respiratory disease and with low antibody titres (measured in a sensitive test system such as ELISA) may be used. Vaccinate the ewes at the stages of pregnancy and according to the schedule to be recommended. A challenge study is conducted with 20 newborn, colostrum-deprived lambs. 10 of these lambs are given colostrum from the vaccinated ewes and 10 control lambs are given colostrum or colostrum substitute without detectable antibodies to *M. haemolytica*. When the lambs are at the age to be claimed for the duration of the passive protection, challenge each by the intratracheal route with a sufficient quantity of a low-passage, virulent strain of a serovar of

M. haemolytica. Observe the lambs for a further 7 days; to avoid unnecessary suffering, severely ill lambs are euthanised and are then considered to have died from the disease. Observe the lambs and assess the effect of the challenge on the offspring of the vaccinates and the controls as described in the test for active immunisation.

The test is not valid if signs or lesions of *M. haemolytica* infection occur in less than 70 per cent of the control lambs. The vaccine complies with the test if there is a significant difference between the scores obtained for the clinical and post-mortem observations in the lambs from the vaccinates compared to those from the controls. For vaccines with a claim for a beneficial effect on the extent of infection against the serovar, the results for the infection rates are also significantly better for the lambs from the vaccinates compared to those from the controls.

2-3 MANUFACTURER'S TESTS

2-3-1 Batch potency test

It is not necessary to carry out the relevant potency test or tests (section 3-3) for each batch of vaccine if they have been carried out using a batch of vaccine with a minimum potency. Where the relevant test or tests are not carried out, an alternative validated method is used, the criteria for acceptance being set with reference to a batch of vaccine that has given satisfactory results in the test(s) described under Potency.

2-3-2 Bacterial endotoxins

A test for bacterial endotoxins (*2.6.14*) is carried out on the final lot or, where the nature of the adjuvant prevents performance of a satisfactory test, on the bulk antigen or the mixture of bulk antigens immediately before addition of the adjuvant. The maximum acceptable amount of bacterial endotoxins is that found for a batch of vaccine that has been shown satisfactory in safety tests 2-2-1-1 given under Choice of vaccine composition. The method chosen for determining the amount of bacterial endotoxin present in the vaccine batch used in the safety test for determining the maximum acceptable level of endotoxin is used subsequently for testing of each batch.

3 BATCH TESTS

3-1 Identification

The vaccine contains the antigen or antigens stated under Definition.

3-2 Bacteria and fungi

The vaccine, including where applicable the diluent supplied for reconstitution, complies with the test for sterility prescribed in the monograph *Vaccines for veterinary use (0062)*.

3-3 Potency

The vaccine complies with the requirements of the test or test(s) mentioned under Immunogenicity (section 2-2-2) when administered by a recommended route and method.