vaccine complies with the test if no chicken shows notable clinical signs of disease or dies from causes attributable to the vaccine.

3.6. Virus titre. Titrate the vaccine virus by inoculation into suitable cell cultures (5.2.4) or eggs from an SPF flock (5.2.2). The vaccine complies with the test if 1 dose contains not less than the minimum virus titre stated on the label.

3.7. Potency. The vaccine complies with the requirements of the tests prescribed under Immunogenicity (sections 2-4-3-1 and 2-4-3-2) when administered by a recommended route and method. It is not necessary to carry out the potency test for each batch of the vaccine if it has been carried out on a representative batch using a vaccinating dose containing not more than the minimum virus titre stated on the label.

4. LABELLING

The label states to which extent the vaccine virus causes disease if it spreads to susceptible young chicks.

01/2005:1944

MANNHEIMIA VACCINE (INACTIVATED) FOR CATTLE

Vaccinum mannhemiae inactivatum ad bovidas

DEFINITION

Mannheimia vaccine (inactivated) for cattle is a preparation from cultures of one or more suitable strains of Mannheimia haemolytica (formerly Pasteurella haemolytica). This monograph applies to vaccines intended for administration to cattle of different ages for protection against respiratory diseases caused by M. haemolytica.

PRODUCTION

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 contain an adjuvant and may be freeze-dried.

CHOICE OF VACCINE COMPOSITION

The choice of composition and the strains to be included in the vaccine is based on epidemiological data on the prevalence of the different serovars of M. haemolytica and on the claims being made. The vaccine is shown to be satisfactory with respect to safety (5.2.6) and efficacy (5.2.7) in cattle. As part of the studies to demonstrate the suitability of the vaccine with respect to these characteristics the following tests may be carried out.

Safety

A. The test is carried out for each route of administration to be stated on the label and in animals of each category for which the vaccine is intended.

For each test, use not fewer than 10 animals that preferably do not have antibodies against the serovars of M. haemolytica or against the leucotoxin present in the vaccine. Where justified, animals with a known history of no previous mannheimia vaccination and with low antibody titres (measured in a sensitive test system such as an ELISA) may be used.

Administer to each animal a double dose of vaccine containing not less than the maximum potency that may be expected in a batch of vaccine. Administer a single dose of vaccine to each animal after the recommended interval. Observe the animals for at least 14 days after the last administration. 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 animal. No abnormal local or systemic reaction occurs; the average body temperature increase for all animals does not exceed 1.5 °C and no animal shows a rise greater than 2 °C. If the vaccine is intended for use or may be used in pregnant cows, vaccinate the cows at the relevant stages of pregnancy and prolong the observation period until 1 day after parturition.

The vaccine complies with the test if no animal shows abnormal local or systemic reactions or clinical signs of disease or dies from causes attributable to the vaccine. In addition, if the vaccine is intended for use in pregnant cows, no significant effects on the pregnancy and offspring are demonstrated.

B. The animals used for the field trials are also used to evaluate safety. Carry out a test in each category of animals for which the vaccine is intended. Use not fewer than 3 groups of 20 animals 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 animal shows abnormal local or systemic reactions or clinical signs of disease or dies from causes attributable to the vaccine. The average body temperature increase for all animals does not exceed 1.5 °C and no animal shows a rise greater than 2 °C. In addition, if the vaccine is intended for use in pregnant cows, no significant effects on the pregnancy and offspring are demonstrated.

Immunogenicity. As part of the studies to demonstrate the suitability of the vaccine with respect to immunogenicity, the test described under Potency may be carried out for each proposed route of administration and using vaccine of minimum potency.

BATCH TESTING

Batch potency test. The test described under Potency is not carried out for routine testing of batches of vaccine. It is carried out, for a given vaccine, on one or more occasions, as decided by or with the agreement of the competent authority. Where the test is not carried out, a suitable validated test is carried out, the criteria for acceptance being set with reference to the results obtained with a batch of vaccine that has given satisfactory results in the test described under Potency.

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 test A given under Choice of vaccine composition or in the safety test described under Tests, carried out using 10 animals. Where the latter test is used, note the maximum temperature increase for each animal; the average body temperature increase for all animals does not exceed 1.5 °C. 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.

**IDENTIFICATION**

When injected into healthy seronegative animals, the vaccine stimulates the production of specific antibodies against the serovars of *M. haemolytica* and/or against the leucotoxin present in the vaccine.

**TESTS**

**Safety.** Use 2 cattles of the minimum age recommended for vaccination that have not been vaccinated against *M. haemolytica*. Administer a double dose of vaccine to each animal by a recommended route. Observe the animals for 14 days. Record body temperature the day before vaccination, at vaccination, 2 h, 4 h and 6 h later and then daily for 2 days. The animals remain in good health and no abnormal local or systemic reaction occurs; a transient temperature increase not exceeding 2 °C may occur.

**Sterility.** It complies with the test for sterility prescribed in the monograph on *Vaccines for veterinary use* (0062).

**POTENCY**

Carry out a test for each serovar for which protection is claimed on the label.

Use not fewer than 16 animals of the minimum age recommended for vaccination, free from antibodies against *M. haemolytica*. Vaccine not fewer than 8 of the animals by a recommended route and according to the recommended schedule. Keep 8 animals as controls. 21 days after the last vaccination, challenge all the animals by the intratracheal route or by another appropriate route, with a suitable quantity of a low-passage, virulent strain of a serovar of *M. haemolytica*. Observe the animals for a further 7 days; to avoid unnecessary suffering, severely ill animals are killed and are then considered to have died from the disease. During the observation period, the animals are examined for signs of disease for example, increased body temperature, dullness, abnormal breathing and the mortality is recorded. Kill surviving animals at the end of the observation period.

Post-mortem examination is carried out on any animal that dies and those killed at the end of the observation period. The lungs and the extent of lung lesions due to *M. haemolytica* are evaluated. Samples of lung tissue are collected for re-isolation of the challenge organisms. The clinical observations and lung lesions are scored and the results obtained for these parameters and the bacterial re-isolation results compared for the 2 groups.

The test is invalid if signs of *M. haemolytica* infection occur in less than 70 per cent of the control animals.

The vaccine complies with the requirements of 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.

**LABELLING**

The label states:

- the serovar(s) of *M. haemolytica* against which protection is claimed,
- the serovar(s) of *M. haemolytica* and/or the leucotoxin present in the vaccine.

**DEFINITION**

Mannheimia vaccine (inactivated) for sheep is a preparation of one or more suitable strains of *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*). This monograph applies to vaccines intended for administration to sheep for active immunisation and to protect passively their future progeny against disease caused by *M. haemolytica*.

**PRODUCTION**

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 contain an adjuvant and may be freeze-dried.

**CHOICE OF VACCINE COMPOSITION**

The choice of composition and the strains to be included in the vaccine is 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) in sheep. As part of the studies to demonstrate the suitability of the vaccine with respect to these characteristics the following tests may be carried out.

**Safety**

A. The test is carried out for each of the routes of administration to be stated on the label and in animals of each category (for example, young sheep, pregnant ewes) for which the vaccine is intended.

For each test, use not fewer than 10 animals that preferably do not have antibodies against the serovars of *M. haemolytica* or against the leucotoxin present in the vaccine. Where justified, animals with a known history of no previous mannheimia vaccination and with low antibody titres (measured in a sensitive test system such as an ELISA) may be used.

Administer to each animal a double dose of vaccine containing not less than the maximum potency that may be expected in a batch of vaccine. Administer a single dose of vaccine to each animal after the recommended interval. Observe the animals for at least 14 days after the last administration. 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 animal. No abnormal local or systemic reaction occurs; the average body temperature increase for all animals does not exceed 1.5 °C and no animal shows a rise greater than 2 °C. If the vaccine is intended for use or may be used in pregnant ewes, vaccinate the ewes at the relevant stages of pregnancy and prolong the observation period until 1 day after lambing.