5.2.7. Evaluation of efficacy of veterinary vaccines and immunosera

The term “product” means either a vaccine or an immunoserum throughout the text. During development of the product, tests are carried out to demonstrate that the product is efficacious when administered by each of the recommended routes and methods of administration and using the recommended schedule to animals of each species and category for which use of the product is to be recommended. The type of efficacy testing to be carried out varies considerably depending on the particular type of product.

As part of tests carried out during development to establish efficacy, the tests described in the Production section of a monograph may be carried out; the following must be taken into account.

The dose to be used is that quantity of the product to be recommended for use and containing the minimum titre or potency expected at the end of the period of validity. For live vaccines, use vaccine containing virus/bacteria at the most attenuated passage level that will be present in a batch of vaccine.

For immunoserum, if appropriate, the dose tested also contains minimum quantities of immunoglobulin or gammaglobulin and/or total protein.

The efficacy evidence must support all the claims being made. For example, claims for protection against respiratory disease must be supported by at least evidence of protection from clinical signs of respiratory disease. Where it is claimed that there is protection from infection this must be demonstrated using re-isolation techniques. If more than one claim is made, supporting evidence for each claim is required.

Vaccines. The influence of passively acquired and maternally derived antibodies on the efficacy of a vaccine is adequately evaluated. Any claims, stated or implied, regarding onset and duration of protection shall be supported by data from trials. The efficacy of each of the components of multivalent and combined vaccines shall be demonstrated using the combined vaccine.

Immunosera. Particular attention must be paid to providing supporting data for the efficacy of the regime that is to be recommended. For example, if it is recommended that the immunoserum needs only to be administered once to achieve a prophylactic or therapeutic effect then this must be demonstrated. Any claims, stated or implied, regarding onset and duration of protection or therapeutic effect must be supported by data from trials. For example, the duration of the protection afforded by a prophylactic dose of an antiserum must be studied so that appropriate guidance for the user can be given on the label.

Studies of immunological compatibility are undertaken when simultaneous administration is recommended or where it is a part of a usual administration schedule. Wherever a product is recommended as part of an administration scheme, the priming or booster effect or the contribution of the product to the efficacy of the scheme as a whole is demonstrated.

LABORATORY TESTS

In principle, demonstration of efficacy is undertaken under well-controlled laboratory conditions by challenge of the target animal under the recommended conditions of use. In so far as possible, the conditions under which the challenge is carried out shall mimic the natural conditions for infection, for example with regard to the amount of challenge organism and the route of administration of the challenge.

Vaccines. Unless otherwise justified, challenge is carried out using a strain different from the one used in the production of the vaccine.

If possible, the immune mechanism (cell-mediated/humoral, local/general, classes of immunoglobulin) that is initiated after the administration of the vaccine to target animals shall be determined.

Immunosera. Data are provided from measurements of the antibody levels achieved in the target species after administration of the product, as recommended. Where suitable published data exist, references are provided to relevant published literature on protective antibody levels and challenge studies are avoided.

Where challenges are required, these can be given before or after administration of the product, in accordance with the indications and specific claims to be made.

FIELD TRIALS

In general, results from laboratory tests are supplemented with data from field trials, carried out, unless otherwise justified, with untreated control animals. Provided that laboratory tests have adequately assessed the safety and efficacy of a product under experimental conditions using vaccines of maximum and minimum titre or potency
5.2.9. EVALUATION OF SAFETY OF EACH BATCH OF VETERINARY VACCINES AND IMMUNOSERA

The term “product” means either a vaccine or an immunoserum throughout the text.

Definition of abnormal reactions. During development studies, the type and degree of reactions expected after administration of the product are defined in the light of safety testing. This definition of normal or abnormal local and systemic reactions is then used as part of the operation procedure for the batch safety test to evaluate acceptable and unacceptable reactions.

Amount to be administered in the test. In the tests, “dose” means the quantity of the product to be recommended for use and containing the titre or potency within the limits specified for production batches. The amount to be administered in the test is usually defined in a number of doses. For freeze-dried vaccines, the 10 doses are reconstituted in a suitable volume for the test. For products consisting of a container of freeze-dried live component(s) and a container of inactivated component(s) to be used as a diluent, it may be necessary to use further liquid for the reconstitution of the freeze-dried component(s). The contents of 2 containers of inactivated component mixed with the contents of a maximum number of freeze-dried live containers are to be injected in one site and the other live freeze-dried components reconstituted using a suitable solvent may be given at a separate site, if necessary and justified. For combined vaccines, safety tests carried out on the combined vaccine may be regarded as sufficient to demonstrate the safety of the individual components.

Route of administration. The product is administered by a recommended route. In principle, preference should be given to the application route with the higher possibility to detect reactions.

Where it is known, for example from development studies, that there is a particular risk, a 2nd administration is performed using a suitable dose and time interval as determined during development.

Target animal species and category of animals. Use animals of the minimum age recommended for vaccination or administration of the product and of the most sensitive species, unless otherwise justified and authorised.

Animal numbers. The number of animals to be used for the test is prescribed in the monographs. Generally 2 animals are used for a mammalian species and 10 for birds and fish.

Identification of animals. Unless otherwise justified, all animals are marked in a suitable way to ensure individual documentation of data for the whole observation period.

Observation period. Where objective criteria such as body temperature are to be recorded as described below, the animals are examined and observed for at least 3 days prior to administration of the product. After administration of the product, the animals are observed and examined at least once every day for a period of at least 14 days for signs of local and systemic reactions. On the day of administration of the product, at least one additional inspection is necessary after 4 h or at intervals as specified in the monograph. Where there is a 2nd administration of the product the period usually ends 14 days after the 2nd administration.

Local and systemic reactions. Animals showing severe abnormal local or systemic reactions are killed. All dead animals undergo a post-mortem with macroscopic examination. Additional microscopic and microbiological investigations may be indicated.

The animals are observed and examined for signs of local and systemic reactions. Where it is known to be a useful indicator, other criteria are recorded, such as body temperature, body mass, other performance measurements and food intake.

Local reactions. As far as appropriate and possible, the size and persistence of any local reaction (including incidence of painful reactions) and the proportion of animals showing local reactions are recorded.

Systemic reactions. Body temperature and if appropriate, body mass are documented as general indicators of systemic effects of administration of the product. In addition, all clinical signs are recorded.

Body temperature. For mammals, the studies include measurement of body temperature during the observation period. The body temperatures are recorded beginning at least 3 days before administration of the product, at the time of administration, 4 h after and at suitable intervals. The body temperature before administration of the product has to be within the physiological range. At least for products where a significant increase in body temperature may be expected (e.g. endotoxin containing products or several live viral vaccines) or is specified in an individual monograph (e.g. not more than 2 °C for porcine actinobacillosis vaccine) it is recommended to use the mean temperature of the days before administration of the product (e.g. day −3 to day 0) as the base line temperature to have clear guidance for evaluation of the test.

Body mass and food intake. Where it is known to be a reliable and useful indicator of safety, for example in young growing animals or in fish, the body mass is measured and documented shortly before administration and during the observation period. The food intake is monitored and documented as an indicator of the effect of administering the product. In most cases, it will be sufficient to record the daily ration has been consumed or partly or wholly rejected but, in some cases it may be necessary to record the actual weight of food consumed, if this is a relevant indicator of the safety of the product.

Clinical signs. All expected and unexpected clinical signs of a general nature are recorded, including changes in health status and behaviour changes.

Score sheets. The score sheets are prepared for each product in the light of expected signs. All parameters and data are recorded in score sheets. The score sheets contain general parameters but are also adapted for each kind of product to list clinical signs which might be more evident for a given product.

Criteria for repeating the test. If an abnormal sign occurs, the responsible veterinarian determines, based on post-mortem examination if necessary, whether this was due to the product or not. If it is not clear what caused the abnormal sign or where an animal is withdrawn for reasons unrelated to the product, the test may be repeated. If in the 2nd test, there is the same abnormal sign as in the 1st test, the product does not comply with the test. Any treatment