



The European Agency for the Evaluation of Medicinal Products  
*Veterinary Medicines and Information Technology*

**EMEA/CVMP/852/99 – FINAL**

**COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS**

**NOTE FOR GUIDANCE**

**FIELD TRIALS WITH VETERINARY VACCINES**

DISCUSSION IN IWP	FEBRUARY 2000
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	7-9 MARCH 2000
TRANSMISSION TO INTERESTED PARTIES	MARCH 2000
DEADLINE FOR COMMENTS	30 SEPTEMBER 2000
ADOPTION BY CVMP FOLLOWING CLOSE OF CONSULTATION PERIOD	13 JUNE 2001
DATE FOR COMING INTO EFFECT	1 DECEMBER 2001

Public

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EMEA 2001

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## **FIELD TRIALS WITH VETERINARY VACCINES**

### **1. Introduction**

The efficacy and safety of veterinary vaccines shall in the first instance normally be demonstrated by experiments under laboratory conditions.

Council Directive 81/852/EEC and the European Pharmacopoeia state that, unless justified, the results from laboratory trials shall be supplemented with data from field trials. It is also stated that, when efficacy cannot be demonstrated by laboratory trials, field efficacy trials alone may be acceptable.

There are two main reasons for carrying out field trials with veterinary vaccines:

- a. The verification that the results of the efficacy and safety trials, under field conditions and on a large scale, reflect those observed in the laboratory trials with the target animals.
- b. The investigation of efficacy items that cannot be studied sufficiently well under laboratory conditions in the target animals. Examples of such items are:
  - Diseases where a suitable experimental infection model does not exist.
  - Certain diseases caused by more than one causal agent.
  - Cases where special husbandry facilities are involved (e.g. drinking water vaccines for poultry, water qualities and temperatures for fish vaccines).
  - Certain diseases where environmental factors play a major role in the aetiology.

Deviations from these guidelines may be acceptable provided they are scientifically justified. The guidance should be followed for products intended for use in food-producing and companion animals.

### **2. Scope of the guidance**

The scope of this guidance is to advise on how to perform field trials with veterinary vaccines, what criteria shall be taken into account, what data are expected and how the data shall be analysed.

This document covers in particular field efficacy trials and, where relevant, safety trials.

### **3. Definition**

For the purpose of this guidance the following definitions apply:

**Field trial:** A scientific investigation of a veterinary vaccine under field conditions and in target animals (in terms of animal species and categories), using the product as recommended.

**Comparator Product:** A product that has been authorised in accordance with the EU requirements with similar indications and recommendations for use and used accordingly.

### **4. Implementation of field trials**

Directive 81/852/EEC and EU guideline "Good clinical practice for the conduct of clinical trials on veterinary medicinal products in the European Union" give the basic standards for the conduct of field trials with veterinary vaccines.

Such trials shall be well planned, controlled and monitored as well as carried out in representative animal houses/husbandry practices and geographical regions. The trials shall follow a study plan made beforehand.

Field trials shall at least cover the major uses. The vaccines shall be administered by the most critical route (e.g. intranasal), method (e.g. spray) and regimen of vaccination to be recommended in the most relevant category of target species. It may not be necessary to include all recommendations, provided that sufficient data from laboratory trials are supplied to cover all uses of the vaccine not included in field trials.

#### **4.1. Field efficacy trials**

Normally one dose of vaccine used shall not contain significantly more than the minimum titre of the vaccine agent(s) or batch potency(ies) to be stated on the label and, for live vaccines, the vaccine agent(s) shall be at the highest attenuated passage level that will be present in a batch of the vaccine. Provided that sufficient data have been presented for all efficacy aspects from laboratory trials using batches of vaccines with minimum titre or batch potency, the use of a batch of vaccine with an intermediate titre or batch potency shown to be representative of those found in routine production of the vaccine is acceptable.

Whenever possible, the field trial shall include the challenge of vaccinated animals by exposure to natural infection. However, it is recognised that a natural infection can neither be predicted nor standardised. It may not appear at the appropriate time and may be too weak or too low in incidence or, in the case of multivalent vaccine testing, not all natural challenges may occur in the study timeframe. Intercurrent infections with the same or other complicating pathogens may also occur.

#### **4.1.1. Parameters**

The parameters to be measured shall be clearly defined in the study protocol and justified in relation to the indications and specific claims for the vaccine.

Conversely, justification shall be given for not measuring parameters that are usually related to the disease concerned.

Two types of parameters exist: the main parameters (e.g. mortality, morbidity, lesions, weight gain, epizootiological impact) and the indicators (e.g. serological response).

For an indicator to be acceptable as a correlate of vaccine efficacy, it shall be shown that a sufficient qualitative and quantitative correlation exists between the indicator measured and the claimed protection in the target species.

If relevant and available, test methods shall be employed that can differentiate naturally infected from vaccinated animals.

#### **4.1.2. Controls and trial design**

The trial shall, unless justified, compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls.

Where vaccination of whole herds is proposed the need for this shall be justified. In such cases, comparison with animals vaccinated with a comparator product may be used when available. For modified live vaccines, whose vaccine agent(s) spread, it is necessary to separate vaccinates from controls. In such cases separate housing of these both groups is justified.

The choice of the controls shall be justified. It is necessary to define in the study protocol what purpose the control group serves. This shall include:

- Evidence that exposure to infection took place.
- A group of animals against which the vaccinated animals can be compared in a valid manner.

For such a comparison to be valid:

- The controls and vaccinated animals shall be as contemporaneous as possible, preferably investigated at the same time;
- The animals of both groups have to be randomised according to the experimental unit;<sup>a</sup>
- The environment in which the two groups of animals are housed shall be as equivalent as possible (i.e. same farm/ barn/batch) or at least as similar as possible (e.g. same farm/different barn/same batch);

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<sup>a</sup> An experimental unit has to be defined in the protocol and is the smallest number of animals in a defined environment on which a statistical analysis can be based.

- The challenge infection shall be as similar as possible in the two groups of animals. This will not be the case if cohorts consist of exclusively vaccinated animals or controls. In this case, repetition of the trials under the same conditions is necessary, using truly randomised groups. The rearing of both groups together may affect the infection rate.

The use of historical data for control purposes is rarely acceptable but where they are used they shall have been shown to be consistent over a representative length of time and well documented.

When investigating a combined vaccine, the control group may comprise animals vaccinated with a product formulated to contain all the components of the vaccine except the component under study.

Ideally, the trials shall be double blind, placebo controlled, but this is often difficult to realise in practice. The need for placebo controls depends on the study plan. If the parameter to be measured is a subjective one (e.g. coughing), then the trial must be done in a blind manner and either placebo controls shall be included or the person who measures this parameter shall have no information on the details of the vaccination.

It is recognised that in some circumstances (e.g. enzootic diseases) inclusion of controls may be difficult. However, even when this is not possible, sufficient evidence shall be presented that the vaccine is having a demonstrable beneficial effect.

#### **4.1.3. Comparator product**

The comparator product and the vaccine under study should claim the same indication.

When the vaccine under study is being compared with a comparator product, a group of controls shall still be included whenever possible. Even if this is not possible, sufficient evidence shall be presented that both products are having a demonstrable beneficial effect rather than just comparing the results of the two groups of animals.

#### **4.1.4. Exposure to infection**

Clear evidence that the vaccinated animals and controls have been exposed to the concerned pathogen shall be given. In principle, the level and moment of exposure shall be the same in both groups of animals. Observation of signs of disease is rarely sufficient by itself and clinical records shall be supported by laboratory tests. In principle, the agent(s) itself shall be detected and identified. In the case of live vaccines, the isolated field strains shall, whenever possible, be differentiated from the vaccine strains. Serology, performed on a statistically sufficient number of animals, may be a supportive measure to demonstrate the exposure to infection. Care must be taken as this may be open to different interpretation. The serological method(s) used shall be validated and the same as used in the laboratory trials.

The causes of any deaths or unexpected signs of disease related to the parameters being measured shall be determined, unless justified. In avian industrial production, standard procedures for diagnosis should be used to determine the cause of death.

If justified, some of the vaccinated animals may undergo an experimental challenge under laboratory conditions, but shall be shown not to have been naturally infected beforehand.

#### **4.1.5. Intercurrent infections**

Infections with intercurrent agents other than those under study that may influence the parameters being measured, might affect the outcome of the trial. Such an influence on the trial can be reduced considerably if the vaccinated and control animals are investigated contemporaneously and allocation of both groups of animals has been made at random.

#### **4.1.6. Pre-existing antibodies**

Pre-existing antibodies against the agent(s) of the vaccine may be:

- Maternally derived.
- Due to infection.
- Due to vaccination.

If the indication or specific claims for the vaccine are related to efficacy in the presence of maternal antibodies against the vaccine agent (s), the trial protocol shall include animals with titres of these antibodies normally occurring in the field.

Where pre-existing antibodies due to previous exposure to the concerned or related agents are present, the trial can still be acceptable if the immunological status of the vaccinated animals and controls at the time of vaccination is known and a justification for their use is given.

In all cases, field trials shall not be carried out in animals that have been vaccinated with products containing the same active substances as the vaccine under study.

#### **4.2. Field safety trials**

For field safety trials, one dose of vaccine shall not contain significantly less than the maximum titre of the vaccine agent(s) or batch potency to be stated on the label and, for live vaccines, the vaccine agent(s) shall be at the lowest attenuated passage level that will be present in a batch of the vaccine.

The field safety trials are, in the first instance, to verify the safety of the vaccine under field conditions after one administration of one dose of vaccine as well as after repeated administration (s) depending on the recommendations.

Part of the data on the safety of the vaccine may be generated from the field efficacy trials.

#### **4.2.1. Parameters**

Field safety trials shall be designed to detect both local and systemic reactions to vaccination.

Field trials are also used to investigate the possible side-effects of vaccination with the product in relation to special items, if relevant. Examples of such systemic effects include allergic reactions, mortality, anorexia, pyrexia, changes in behaviour, weight gain, feed conversion, carcass quality, milk/wool/fur production, egg production and hatchability of breeding eggs and male and female fertility. In the case of live vaccines, the behaviour of the vaccine agent(s) in animal populations should be documented. In terms of local reactions, the size, duration and nature of any lesions appearing at the sites of injection shall be monitored and recorded.

#### **4.2.2. Controls and trial design.**

The trial shall normally compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls.

The choice of the controls shall be justified. The control group shall comprise animals against which the vaccinated animals can be compared in a valid manner.

See further, where relevant, paragraph 4.1.2.

#### **4.3. Animal welfare Considerations**

Field trials can have implications of importance for animal welfare. The inclusion of control animals may lead to an increase in the prevalence of the disease . However, it is important to recognise that the use of controls holds the promise of preventing or reducing the future incidence of the disease through the release of efficacious vaccines. Furthermore, carrying out field trials in animals under normal husbandry conditions may reduce the number of animals needed for laboratory trials.

Special care should therefore be taken with the study plan in order to respect animal welfare when carrying out such studies.

#### **5. Analysis and interpretation**

According to Council Directive 81/852/EEC all available data of field trials shall be included in the dossier of the Application for a Marketing Authorisation. Only data of valid field trials may support such an Application and in particular all relevant details should be given of any incomplete or abandoned test or trial.

The analysis of the data of field efficacy trials shall be related to the Indication and specific claims made for the vaccine and the parameters measured (see Position paper on indications and specific claims for immunological veterinary products).

The analysis of the data of field safety trials shall be related to the recommendations for the administration of the vaccine.

Careful consideration shall be especially given to:

- The study plan.
- The plan for analysis.
- The evaluation of the data.
- The statistical evaluation, including confidence limits, of the data.
- The hypothesis for risk of errors.
- The randomisation of the various groups of animals.
- The number of animals required, including eventual losses during the trial.

In the case of efficacy as judged by serology, the titres measured in vaccinated animals shall be not significantly lower in the target animals used in the field trials than those in the laboratory trials. In the case of a marker vaccine, special attention should be paid to properties of the marker.

## **6. Deviations from the basic principle**

In cases of vaccines against notifiable and /or exotic animal diseases for which vaccination is not allowed in the European Union, it may be difficult to find other suitable areas to carry out the required field trials. In such cases the need for extensive laboratory trials may be increased. Such cases are judged on an individual basis to determine if there is a zoo-sanitary legal requirement to restrict the efficacy and safety investigations to laboratory trials. Data from field trials conducted outside the EU, especially if conducted according to Good Clinical Practice, may be considered in support of applications for such vaccines.

When the vaccine is intended against an animal disease that occurs only rarely and sporadically in the field and where a suitable laboratory test model exists, it may be acceptable under certain conditions to limit the requirement for field efficacy trials. Such cases shall also be judged on an individual basis. In such cases the need for extensive laboratory trials may also be increased.

In cases where the vaccine is intended for use in minor species, a limitation of the field trial requirements may be considered. Justification shall be given and the decision made on an individual basis.

In the circumstance where a side-effect occurs very rarely (e.g. allergic reactions) extensive post marketing surveillance rather than extended field trials may be considered for the purpose of gaining a Marketing Authorisation for the vaccine.