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Guideline on clinical trials with immunological veterinary medicinal products

Draft

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This guideline replaces the Note for Guidance 'Field trials with veterinary vaccines' (EMEA/CVMP/852799-Final).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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Guideline on clinical trials with immunological veterinary medicinal products

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Executive summary

The main aim of the guideline is to advise on how to perform clinical trials (also called field trials) with immunological veterinary medicinal products (IVMPs) and to address the requirements of the Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council regarding clinical trials for IVMPs.

In addition, guidance is provided on when omission of clinical efficacy data may be acceptable.

This guideline replaces the Note for Guidance 'Field trials with veterinary vaccines' (EMEA/CVMP/852799-Final).

1. Introduction (background)

The efficacy and safety of IVMPs shall normally be demonstrated by studies under laboratory conditions (pre-clinical studies).

Clinical safety trials should be performed in order to verify results of pre-clinical safety studies, under field conditions and on a large scale.

With respect to clinical efficacy, Annex II to Regulation (EC) 2019/6 (section IIIb, Requirements for Immunological Veterinary Medicinal Products) states that, whereas results of trials carried out in field conditions are generally required to support pre-clinical studies, clinical efficacy trials may not be required in those cases when pre-clinical studies fully support the claims made in the summary of product characteristics. It is also stated that, where pre-clinical studies cannot be supportive of efficacy, the performance of clinical (field) trials alone may be acceptable.

2. Scope

Guidance is provided on how to perform clinical trials with IVMPs, what criteria shall be taken into account, what data are expected and how data shall be analysed. The advice covers in particular clinical efficacy trials and, where relevant, clinical safety trials.

The guideline also concerns in particular criteria that may be applied in order to decide on the need to generate and provide clinical efficacy data.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with Annex I and II to Regulation (EU) 2019/6, as amended, and other relevant EU and VICH guidelines as well as European Pharmacopoeia applicable texts and monographs to IVMPs. These include, but are not limited to:

- Position paper on indications for veterinary vaccines (EMEA/CVMP/042/97-Rev.1-FINAL)
- Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/594618/2010)
- Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines (EMA/CVMP/IWP/314550/2010)
- Note for guidance: Duration of protection achieved by veterinary vaccines (EMA/CVMP/682/99)
- VICH GL9 Good clinical practices (CVMP/VICH/595/1998)

- Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010).

4. Requirement to provide field data

4.1. Introduction

Concerning IVMPs, Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EC) 2019/6 details the following:

With respect to safety data:

"Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same clinical trials."

With respect to efficacy data:

"In general, pre-clinical studies shall be supported by trials carried out in field conditions.

When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required.

Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials, using batches representative of the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same clinical trials.

Where pre-clinical studies cannot be supportive of efficacy, the performance of field trials alone may be acceptable."

Based on the text of the regulation, normally, clinical safety studies should be performed and data presented in the dossier for a marketing authorisation. For efficacy, the requirement for provision of field data is less strict and the performance of clinical efficacy studies may be omitted if adequate evidence of efficacy, supporting all claims, can be derived from the pre-clinical efficacy studies.

Clinical trials (field trials) shall be conducted in accordance with established principles of good clinical practice, unless otherwise justified.

4.2. Criteria for the omission of clinical efficacy data

For clinical efficacy data to be omitted from the dossier of a marketing authorisation application, it is considered that the following three criteria should all be met:

a) A highly relevant laboratory model of infection was used and results of the pre-clinical efficacy studies fully support the efficacy claims.

> The laboratory model induces a disease that is comparable to the naturally occurring disease. Comparability is evident with respect to type and frequency of clinical signs, overall disease severity and distribution and/or shedding of the organism(s). The route of infection for the model is similar to the natural infection route. A relevant strain or isolate of the pathogen is used; relevance can be deduced from data on the timing of isolation, location or origin of isolation and data on strain variability and cross protection. Animals used in these studies are relevant for the intended target population, with respect to health status, maternal immunity, age, category and/or breed. If any of the requirements cannot be met, a robust scientific justification must be provided that assures the challenge model is still relevant.

b) The intended method of administration of the vaccine can be fully mimicked under laboratory conditions.

In general, administration of IVMPs should not present a problem for comparability of laboratory data and efficacy in the field. Nevertheless, IVMPs intended for mass administration (e.g. via drinking water) or specific non-standard routes of administration (e.g. alternative injection sites like the lip, inhalers, nose spray or eye drop) may need supportive data from clinical studies to ensure that under field conditions of use proper administration is achieved. Where satisfactory efficacy has been documented in the context of pre-clinical studies, data on the effectiveness of particular administration methods or mass administration under conditions of field use may also be acquired by using correlates of protection or by laboratory challenge of animals taken from clinical safety studies.

c) The pre-clinical efficacy studies are of high quality with respect to design and execution and vaccine effects that are both clinically relevant and statistically significant have been observed.

4.3. Situations when clinical efficacy data is considered necessary

In the following situations, clinical efficacy data is considered necessary for immunological veterinary medicinal products:

- that are claimed to have an epidemiological effect or for which an epidemiological effect is obviously important (e.g. herd immunity).

- that are indicated against vector-transmitted diseases.

An exception can be made if an appropriate laboratory model is used that employs challenge infection via a vector or that has robust scientific data to support that it fully replicates all relevant aspects of vector-mediated infection (for example, but not limited to: presence of saliva or other vector derived substances, low and/or repeated doses, intracutaneous application).

- which are claimed to have an effect on multifactorial disease outcomes.

- that are claimed to have an effect on performance parameters (e.g. weight gain, feed conversion, laying).

4.4. Situations when clinical efficacy data may replace pre-clinical data

Clinical trial data may be accepted instead of data from pre-clinical studies, for immunological veterinary medicinal products:

- where pre-clinical studies cannot be supportive of efficacy because a valid challenge model is not available

- that are claimed to have a long-term duration of protection which cannot be demonstrated by pre-clinical trials due to animal welfare reasons and/or ethical aspects connected with long term holding of animals under laboratory conditions. Bearing in mind that duration of protection after the basic vaccination scheme shall be justified in relation to the length of time for which animals are likely to be at risk, target animals should be vaccinated in the field and undergo thereafter a natural challenge in the field or an experimental challenge under laboratory conditions.

- that are claimed to be efficacious after re-vaccination, if no laboratory vaccination-challenge trials can be conducted after re-vaccination, e.g. due to animal welfare reasons and/or ethical aspects connected with long-term holding of animals under laboratory conditions. Field data would only be

acceptable, if there is a suitable indicator for protection other than challenge. For such an indicator evidence shall be provided to show that the indicator plays a substantial role in the protection of the target species and that there is a sufficient qualitative and quantitative relationship between the indicator and the protection of the target species against the disease concerned. It must be demonstrated (via indicators of protection) that the level of response from re-vaccination scheme can be considered equal to the one observed at the time of challenge used to demonstrate the efficacy after the basic vaccination.

If clinical data should support the duration of immunity or the efficacy of the re-vaccination scheme, it shall be ensured that the vaccinated target animals are not exposed to intercurrent field infection, which could interfere with efficacy e.g. by boosting the immunity. Therefore, it is usually necessary to maintain unvaccinated target animals in contact to act as sentinels.

4.5. Deviations from the basic principles

Deviations from the basic principles as outlined in sections 4.2 and 4.3 may be appropriate in particular cases as described in this section.

When an IVMP is intended for an animal disease that occurs only rarely and sporadically in the field and where the conditions set out in section 4.2 cannot be met, it may be acceptable to omit the requirement for clinical efficacy trials. Such cases are judged on an individual basis and conditions may be set. For instance, more extensive pre-clinical efficacy studies could be necessary.

In cases of IVMPs 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 clinical trials, if required. 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 pre-clinical trials. Data from clinical trials conducted outside the EU, in particular when conducted according to Good Clinical Practice, may be considered in support of applications for such IVMPs.

For IVMPs that are indicated for limited markets reduced data requirements with respect to clinical efficacy data may apply. Guidance on this subject should be consulted.

For IVMPs to be authorised under exceptional circumstances reduced data requirements with respect to clinical efficacy data may be appropriate. Guidance on this subject should be consulted.

5. Assessment of efficacy under field conditions

5.1. Efficacy criteria

The efficacy criteria shall be clearly defined in the study protocol and justified in relation to the indications and specific claims for the IVMP.

Justification shall be given for not including parameters that are known to be related to the disease concerned.

Primary efficacy criteria are generally derived from main disease parameters: mortality, morbidity, clinical signs and/or lesions. Secondary criteria may for example include parameters related to production (e.g. weight gain, egg laying) or infection parameters (e.g. shedding, viraemia).

For an indicator of protection to be acceptable as a correlate of IVMP efficacy, it shall be demonstrated that a sufficient correlation exists between the indicator measured and the claimed protection in the target species. An indicator for protection should be shown to play a substantial role in the immune response, relevant for protection of the target species against the disease concerned.

5.2. Controls and study 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 and the study should be designed to demonstrate non-inferiority. For modified live vaccines, whose vaccine agent(s) spreads, it is necessary to separate vaccinated animals from controls. In such cases separate housing of vaccinated and control groups is justified.

The choice of 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 comparison to be valid:

- The controls and vaccinated animals shall be investigated at the same time. Where this is not possible, justification should be provided.

- The animals of both groups have to be randomised according to the experimental unit

- The environment in which the two groups of animals are housed shall be equivalent (i.e. same farm and barn) or as similar as possible (e.g. different barn on the same farm and with similar set-up).

- Field challenge shall be as similar as possible in the groups of animals. The dynamics of a field infection may not be similar if cohorts consist of exclusively vaccinated animals or negative controls. Therefore, where possible, vaccinated and control groups should be mixed.

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

Ideally, the trials shall be double blind- and placebo-controlled, but this is often difficult to realise in practice. The need for placebo controls depends on the study plan. As a rule, but in particular if the parameter to be measured is subjective (e.g. coughing), any observant and anyone involved in the generation of data (e.g. pathologist, laboratory staff) must be blinded to the treatment.

It is recognised that in some circumstances (e.g. enzootic diseases) inclusion of placebo/non-vaccinated controls may be difficult for reasons of animal welfare. However, even when the inclusion of controls is not possible, sufficient evidence shall be presented that the vaccine is having a demonstrable beneficial effect.

The batch(es) used shall be of standard or intermediate potency or titre whenever safety and efficacy measurements are combined in one clinical study. Alternatively, in case separate trials are performed to determine safety and efficacy in the field, it is expected that minimum titre/potency batches would be used in the efficacy trials in order to maximise the information that can be derived from the studies.

5.2.1. Comparator product

The comparator product should have similar indications and specific claims as those proposed for the IVMP under study.

A study involving a comparator product should be designed as a non-inferiority study. Guidance on the design of non-inferiority studies is available in the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010).

When the IVMP under study is being compared with a comparator product, a group of non-vaccinated or placebo controls shall still be included whenever possible in order to verify field challenge. If this is not possible, sufficient evidence shall be presented that both products are having a demonstrable beneficial effect.

5.2.2. Exposure to infection

Clear evidence that the vaccinated animals and controls have been exposed to the concerned pathogen(s) shall be given. In principle, the study should be designed to allow for a similar level and timing of exposure to the pathogen(s) in both groups of animals. Observation of signs of disease is rarely sufficient by itself and clinical records shall be supported by pre-clinical data. In principle, the agent(s) itself shall be detected and identified. In case of live vaccines, the isolated field strains shall, whenever possible, be differentiated from the vaccine strains. Regular serological testing, performed on a statistically sufficient number of animals, may be a supportive measure to demonstrate exposure to the pathogen. The serological method(s) used shall be validated and the same as used in the pre-clinical studies.

The causes of any deaths or unexpected signs of disease shall be determined using appropriate methods, where possible. It is expected that necropsy is performed in such cases.

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 prior to challenge.

5.2.3. Intercurrent infections

Infections with agents other than those under study that may influence the parameters being measured may affect the outcome of the trial. Such an influence on the trial can be reduced considerably if vaccinated and control animals are investigated in parallel and if randomisation is applied for allocation to study groups.

5.2.4. Pre-existing antibodies

Pre-existing antibodies against the agent(s) in the IVMP may be maternally derived, due to infection or due to prior vaccination.

If the indication or specific claims for the IVMP 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, ensuring that the animals are still susceptible to the infection.

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

6. Clinical safety trials

The clinical safety trials are primarily performed to verify the safety of the IVMP under field conditions after administration of one dose of vaccine as well as after repeated administration(s) depending on the recommendations for use.

6.1. Parameters

Clinical safety trials shall be designed to detect both local and systemic reactions to vaccination. In addition, clinical safety trials provide an opportunity to detect more rare adverse reactions that are unlikely to occur in laboratory studies in a small number of animals.

Parameters used to determine systemic effects of vaccination may 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. Additional or alternative parameters relevant for a specific pathogen may be used, where appropriate and justified.

In case of live vaccines, the behaviour of the vaccine agent(s) in animal populations should be documented (e.g. spread, persistence in the environment).

In terms of local reactions, the size, duration and nature of any reactions appearing at the site of injection shall be monitored and recorded.

6.2. Controls and trial design

The trial shall normally compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls originating from the same target population.

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.

The batch(es) used shall be of standard or intermediate potency or titre whenever safety and efficacy measurements are combined in one clinical study. In case separate clinical safety trials are performed, one dose of IVMP shall not contain significantly less than the maximum titre of the vaccine agent(s) or batch potency to be stated on the label. For live vaccines, the vaccine agent(s) shall be at the least attenuated passage level that will be present in a batch of the IVMP, in order to maximise the information to be derived from the study.

See further, where relevant, paragraph 5.2

7. Animal welfare considerations

Clinical trials should be designed to avoid causing pain, suffering and distress to animals. Whenever possible, alternative -less invasive- test methods should be used and the initiation of rescue treatment based on pre-defined limits for disease parameters should be included in the study plan.

8. Analysis and interpretation

According to Regulation (EU) 2019/6 all available data of clinical trials shall be included in the dossier of the application for a marketing authorisation. Only data of valid clinical trials may support such an application. Nevertheless, all relevant details should be given of any incomplete or abandoned test or trial.

Preferably, the sample size should be calculated a priori, based on the expected effect size and the variance. A clinically relevant effect size should be described a priori.

When efficacy of vaccination is demonstrated by comparison to a positive comparator in a non-inferiority study, a non-inferiority margin should be defined and justified in the study plan.

Guidance on the calculation of sample size and the design on non-inferiority studies can be found in the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010).

The analysis of the data of clinical efficacy trials shall be related to the indication and specific claims made for the IVMP, and the parameters measured (refer to "indications and specific claims for immunological veterinary products").

In the case of efficacy as judged by an indicator of protection, non-inferiority may be demonstrated in comparison to animals vaccinated with a comparator vaccine or in comparison to animals vaccinated (and shown to be protected) in the pre-clinical trials.

The analysis of data of clinical safety trials shall be related to the recommendations for use. 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.

Definitions

Immunological veterinary medicinal product (IVMP): a veterinary medicinal product intended to be administered to an animal in order to produce active or passive immunity or to diagnose its state of immunity.

Clinical trial: A study which aims to examine under field conditions the safety or efficacy of an IVMP under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof. (Synonyms: field efficacy/safety trial).

Pre-clinical study: A study not covered by the definition of clinical trial which aims to investigate the safety or efficacy of an IVMP for the purpose of obtaining a marketing authorisation or a change thereof.

Indicator of protection: For an indicator to be acceptable as a correlate of efficacy for a specific type of vaccine(s), it shall be demonstrated that a sufficient correlation exists between the indicator measured and the claimed protection in the target species. An indicator for protection should be shown to play a substantial role in the immune response, relevant for protection of the target species against the disease concerned. It must be demonstrated that the level of response obtained for the indicator in clinical trials is equal to the one observed in vaccinated animals at the time of challenge in pre-clinical trials and for which protection was demonstrated.

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

Placebo: a substance without therapeutic effect, used as a control substance in pre-clinical or clinical studies.