Regulatory requirements for veterinary vaccines in Europe

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I attend this meeting as an individual expert, and do not represent the CVMP. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CVMP or reflecting the position of the CVMP.

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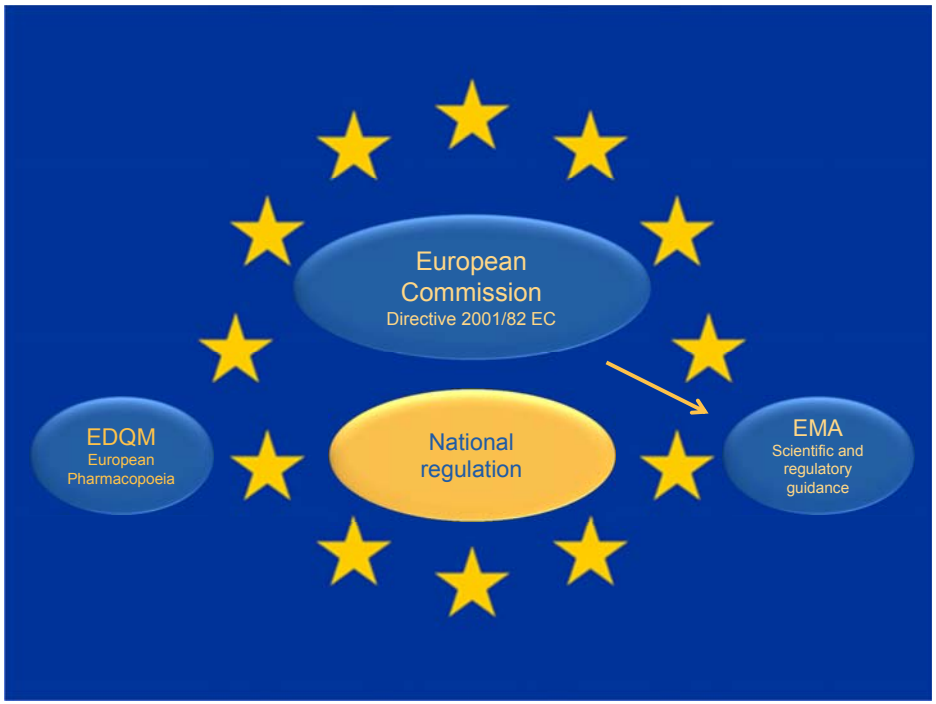

Legal framework for immunological veterinary medicinal products in Europe

Directive 2001/82 EC as amended

Annex 1 title II details requirements for immunological veterinary medicinal products, including field trials. Describes dossier structure and content

DIRECTIVE 2001/82/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 6 November 2001
on the Community code relating to veterinary medicinal products

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European Pharmacopoeia – EDQM (Council of Europe)
General and specific monographs with detailed descriptions and requirements for manufactuting of medicinal products. Focus on quality aspects. Legally binding

Scientific and regulatory guidance – from the committées of EMA (European Medicines Agency)

National Regulations


EUROPEAN MEDICINES AGENCY
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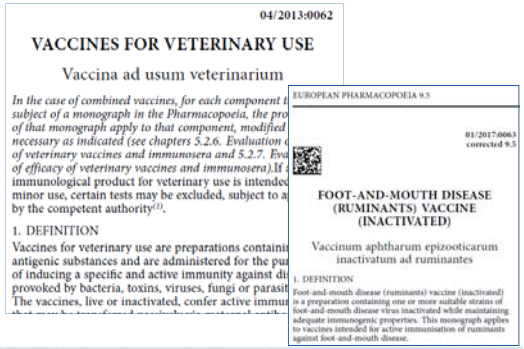
Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)


04/2013:0062

VACCINES FOR VETERINARY USE

Vaccina ad usum veterinarium

EUROPEAN PHARMACOPOEIA 9.5

01/2017:0063 corrected 9.5

FOOT-AND-MOUTH DISEASE (RUMINANTS) VACCINE (INACTIVATED)

Vaccinum aphtharum epizooticarum inactivatum ad ruminantes

1. DEFINITION

Foot-and-mouth disease (ruminants) vaccine (inactivated) is a preparation containing one or more suitable strains of foot-and-mouth disease virus inactivated while maintaining adequate immunogenic properties. This monograph applies to vaccines intended for active immunisation of ruminants against foot-and-mouth disease.

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The basic vaccine concept: it starts in the lab

Traditionally, clinical data for vaccines are first produced in laboratory studies

Described in Ph.Eur. for many known vaccines

- safety evaluation
- in the target animal
- controlled
- standardised
- specific challenge with infectious agent
- detailed follow up

Enables detailed and controlled data in a limited number of animals

However, a challenge model may not

- represent natural conditions fully
- be available (e.g. for new/emerging diseases)

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Safety data

Laboratory studies:

- intended administration (route and schedule)
- Live vaccines 10x overdose

Live vaccines

- spread to other animals
- dissemination within the vaccinated animal
- reversion to virulence

Pregnancy and lactation

Ecotoxicity

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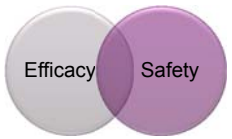
Need for field data

Field data of a sufficiently high standard represent the highest level of proof that a vaccine is able to perform under practical conditions of use



Directive 2001/82 EC

C. FIELD STUDIES

Unless justified, results from laboratory studies shall be supplemented with data from field studies, using batches according to the manufacturing process described in the marketing authorisation application. Both safety and efficacy may be investigated in the same field studies.

Field data should confirm findings from laboratory studies

Evaluate safety/efficacy during use in natural conditions that cannot be fully reproduced in a laboratory setting

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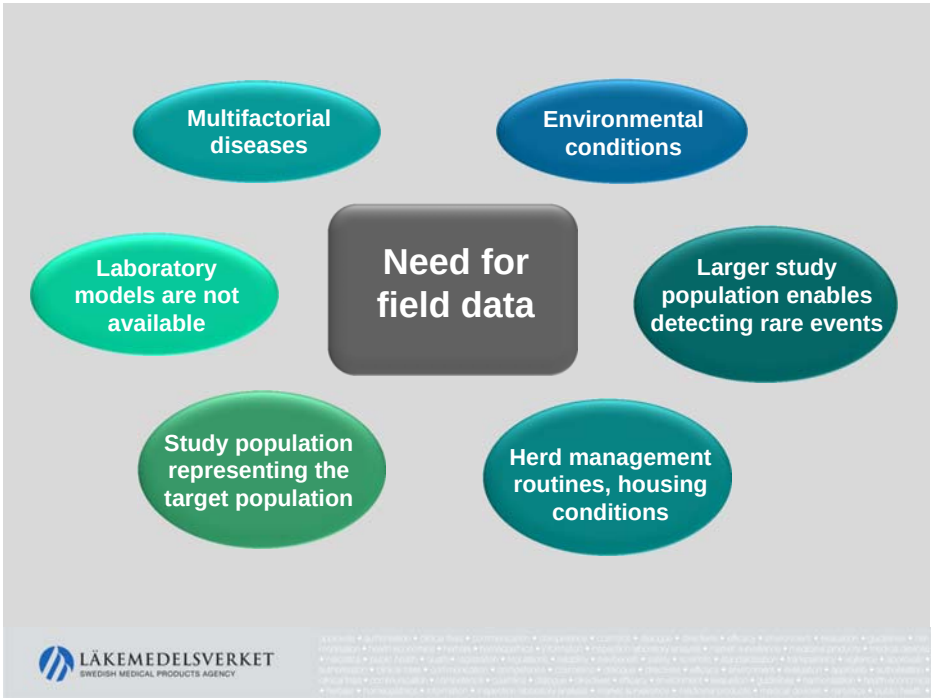


Exceptions to the rule – when field studies are not required

Exceptional circumstances

It is not possible to produce field data during the circumstances, e.g. Bluetongue

Epizootic diseases

Vaccination is prohibited, e.g. FMD, CSF

Exemption is also possible if the product is classified as

MUMS (Minor Use Minor Species)

If e.g. sufficient laboratory data is available or field study is not feasible when the infection/disease is very rare

The need for field efficacy data is discussed

Growing concern from industry: field studies are expensive and difficult to perform but often fail to contribute sustantial/vital information

In many cases field infection is not present → inconclusive

Focus Group meeting on field efficacy trials for veterinary vaccines – Industry, regulators and academic experts

Alternative sources of information

Balancing the need for field data against the possibility of gaining sufficient information from other sources

Possible alternatives	Less suitable alternatives
Well established laboratory challenge models	Pharmacovigilance data (passive)
Epidemiological modelling	Post authorisation studies
Meta-analysis of literature data	
??	

Basic requirements for field trials

- The study population is representative of the target population
- Conditions of the study are representative of the intended use
- An adequate control is included
- Relevant endpoints are evaluated
- The study is dimensioned to provide support for the relevant hypothesis
- Appropriate statistical analysis
- Field infection is demonstrated

Basic study design

Parallel design

Randomised
Blinded
Controlled

Controls

Negative (placebo, untreated)
Positive if a suitable comparator is available (authorised in EU)
Positively controlled study can include negative control group to show internal validity

Mixing vaccinated animals and controls i the same group? Different groups in the same unit? Separate units? Separate farms?

Field vaccination → laboratory challenge. Addresses some aspects but is not a complete field trial

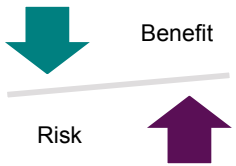
Considerations for study design

What is the purpose of vaccination?

- management of infection in a herd
- prevention of disease in individual animals
- eradication/control programme
- control in an outbreak of epizootic disease

What degree of effect is relevant and needed for this vaccine and under the conditions it will be used?
The Benefit-Risk Balance may differ depending on the situation

How is this best demonstrated?



Parameters for evaluation of efficacy

Relevant parameters depend on the disease/infection

- clinical disease
- pathological lesions
- transmission of infection
- viraemia
- ...

Surrogate markers

- e.g. serology
- demonstrated correlation to effiacy →

  immunogenicity may not equal efficacy!

Epidemiological modelling of efficacy data

Example: Bovilis BTV8

To evaluate effect of vaccination on the risk of bluetongue infection in cattle

Threshold value of viraemia when the chance of infection of the vector (and subsequently other animals) is low to zero was established based on laboratory data for dose-response for reduction of viraemia

Mathematical transmission models building on experimental data and simulating at the population level

Epidemiological modelling of efficacy data

Example: Bovilis BTV8 cont.

→The reduction of viraemia after vaccination is likely to reduce virus transmission to an extent that can limit the spread of an outbreak in a vaccinated population

Models include a range of assumptions – the reliability depends on the correct choice of parameters

The degree of transmission that will occur in a vaccinated population will depend on several factors (animal density, vaccine coverage...) and variation/uncertainty needs to be considered

→ Absolute assurance of lack of transmission cannot be given

Two different models by separate groups – confirmed results

Field Safety data

Confirm data from laboratory studies

- rare events can be detected in a larger population
- target population of animals
- handling and administration
- spread to other species or the environment

Special cases – GMOs, DNA vaccines

Example: Clynav

Genetically Modified Organisms, GMOs

DIRECTIVE 2001/18/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 March 2001

on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC

Definitions

For the purposes of this Directive:

(1) 'organism' means any biological entity capable of replication or of transferring genetic material;

(2) 'genetically modified organism (GMO)' means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;

Genetically Modified Organisms, GMOs

Directive 2001/18/EC

Environmental risk assessment of the release of a GMO into the environment is needed in addition to regular data requirements in the dossier

GMO authorities in each Member States assess

Clinical trials – National regulations in each member state, needs to be approved in each member state where the trial will be conducted

DIVA
Differentiating Infected from Vaccinated Animals

Advantage if epizootic disease

Requires commercially available diagnostic test

Use of field data from other regions

Possible but requires that

- Infection (strain) and other conditions (target animals, management, housing, environmental conditions...) are considered relevant for Europe
- The study is of sufficient quality standard (e.g. GCP)
- Animal welfare concerns are acceptable according to European requirements

→ Case by case decision

Guidance when developing vaccines intended for marketing authorisation

National Competent Authorities

- Scientific and regulatory advice

EMA

- Innovations Task Force
- Scientific Advice
- SME office

Regulatory consultants

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References

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82/dir_2001_82_en.pdf

Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF

CVMP and VICH guidelines for immunologicals http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000374.jsp&mid=WC0b01ac058002ddc5

- Field trials with veterinary vaccines (EMA/CVMP/852/99) https://www.ema.europa.eu/en/field-trials-veterinary-vaccines

- Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/IWP/123243/2006-Rev.3) https://www.ema.europa.eu/documents/scientific-guideline/guideline-data-requirements-immunological-veterinary-medicinal-products-intended-minor-use-minor/limited-market-revision-3_en.pdf

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European Assessment Report for Clynav (EMA/293169/2016) https://www.ema.europa.eu/documents/assessment-report/clynav-epar-public-assessment-report_en.pdf

European Assessment Report for Bovilis BTV8 (EMA/CVMP/234334/2009) https://www.ema.europa.eu/documents/scientific-discussion/bovilis-btv8-epar-scientific-discussion_en.pdf

Focus group with invited stakeholders on field efficacy trials in the context of an EU authorisation for veterinary vaccines https://www.ema.europa.eu/documents/other/report-focus-group-meeting-invited-stakeholders-field-efficacy-trials-context-eu-authorisation_en.pdf

Abbreviations:

EMA	European Medicines Agency
CVMP	Committee for Medicinal Products for Veterinary Use
EDQM	European Directorate for the Quality of Medicines
Ph.Eur	European Pharmacopoiea
SME	micro, Small and Medium-sized Enterprises

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