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Challenges in performing field trials to support efficacy:

Companion animal vaccines

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Legislation and guidelines

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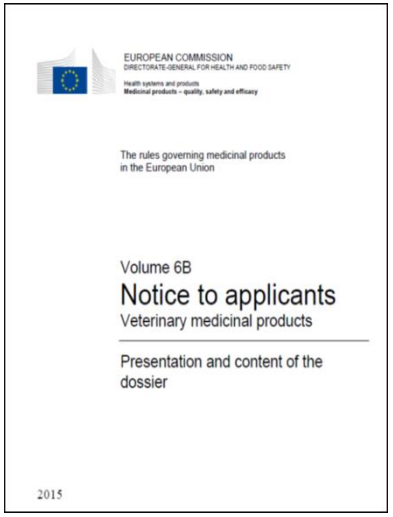
- Annex 1 Directive 2001/82/EC as amended
  - Directive 2009/9/EC
- Volumes 6a and 6b of the European Notice to Applicants
  - Guideline EMA/CVMP/852/99
- Ph. Eur. Vaccines for veterinary use 5.2.7



European Pharmacopoeia

Current requirements on Efficacy

Directive 2009/9/EC, Title II, Part 4, Chapter 1

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Efficacy trials: Vaccines

- **General principles**
  - Purpose of trials
  - Claims fully supported by results of trials
  - Efficacy trials conducted to detailed prtcl
  - Pre-established written procedures
  - Controlled (placebo)
  - **Field trials conducted to GCP, unless justified**
  - Informed consent, animal welfare
  - Labelling: for veterinary field trial use only“

Current requirements on Efficacy

Directive 2009/9/EC, Title II, Part 4, Chapter 2

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Efficacy trials: Vaccines

- **General requirements (cont.)**
  - Justify choice of antigen or vaccine strain
  - Efficacy trials carried out in the laboratory shall be controlled trials, including untreated control animals unless this is not justified for animal welfare reasons and efficacy can be otherwise demonstrated.
  - **In general, these laboratory trials shall be supported by trials carried out in field conditions, including untreated control animals.**
  - All trials described in sufficiently precise details, demonstrating validity of techniques
  - All results obtained, whether favourable or unfavourable, shall be reported.

Current requirements on Efficacy

Directive 2009/9/EC, Title II, Part 4, Chapter 2

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Efficacy trials: Vaccines

- **General requirements (cont.)**
  - Demonstrated for each category of species, each route, proposed schedule
  - Each component and their compatibility
  - Proof of priming or booster effect
  - Proof of minimum potency/titre dose
  - Batch control
  - ...

Current requirements on efficacy

Directive 2009/9/EC, Title II, Part 4,

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Efficacy trials: Vaccines

- **Laboratory trials (Chapter II, B)**
  - Well controlled **laboratory conditions by challenge** to target animal
  - Insofar as possible, shall mimic natural conditions
  - If possible, immune mechanism shall be specified
- **Field trials (Chapter II, C)**
  - Unless justified, results form laboratory trials shall be **supplemented with data from field trials**
  - **Where laboratory trials cannot be supportive of efficacy, performance of field trials alone may be acceptable**

Current requirements on efficacy

Directive 2009/9/EC, Title II, Part 5, C

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Efficacy trials: Vaccines

- **Particulars and documents**
  - **B: Lab studies and C: Field trials**
    - Particulars to be provided shall include the following information
    - …

Current requirements on efficacy

(EMA/CVMP/852/99)

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- **Two main reasons for carrying out field trials with veterinary vaccines:**
  - the verification that the results of the efficacy and safety trials, under field conditions and on a large scale, reflect those observed in the lab trials with the target animals
  - the investigation of efficacy items that cannot be studied sufficiently well under laboratory conditions in the target animals:
    - Diseases where a suitable experimental infections model not exists
    - Certain diseases caused by more than one causal agent
    - Case where special husbandry facilities are involved
    - Certain diseases, where environmental factors play a major role in the aetiology

Current requirements on efficacy

(e.g. Ph. Eur. Vaccines for Veterinary use 5.2.7)

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- **In claims related to S3 or S4 pathogens, field studies not requested (e.g. rabies etc.): for the most relevant diseases, we accept that we do not need field studies: why require them for less critical diseases?**
- **Ph. Eur. Monographs have served for many decades to provide efficacious vaccines: none required field studies for proof of efficacy!**
- **With novel therapies, some immunological products are intended for claims, where no challenge model available and/or Ph.Eur. not available yet: in these cases field trials are the single option to show efficacy and not in question!**

Categories of vaccines for pets

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- **Infectious disease (conventional) e.g. DHPPi, FRC, rabies, Leishmania, Babesia etc.**
  - Usually, models available and provide relevant data on efficacy
  - Claims have been granted for many decades based on such models
  - Ph.Eur. Monographs for many of these diseases and seem to be well accepted as sufficient
- **Non-infectious diseases: e.g. atopy, cancer, obesity etc.**
  - These may bring additional challenges compared to those for infectious disease
  - Field studies may be needed, as no “models” in the target species exist

Challenges with companion animal vaccines

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- **Detection of appropriate clinical-pathological parameters**
- **Low prevalence of some diseases**
  - How to handle emerging diseases
  - Studies to prove claim of “prevention” usually require very high number of animals, long keeping separate
  - In many cases incidence of disease low, especially where already other vaccines marketed
    - Thus difficult to obtain enough statistical power
- **Multivalent vaccines e.g. DHPPi-lepto, PCR etc.**
  - Multiply the problems as outlined above
  - Evidence for efficacy of each component to be proven??

Challenges with companion animal vaccines

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- **Ethics of negative controlled studies**
  - More and more a problem to get consent for conduct of negative controlled studies
  - Positive controls or non-controlled studies??
  - Meaningful results on efficacy?
- **Challenges / complexity / expense of recruiting clinical patients**
  - Working through veterinary practices: with negative controls hardly acceptable in cases of infectious diseases
  - Individually owned animals, trial conduct very cumbe
  - Only option for cases, where no model available

Challenges with companion animal vaccines

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- **Results of field efficacy studies meaningful in vaccines?**
  - Most claims are solely based on effects demonstrated in challenge studies
- **Field efficacy or rather field safety?**
  - Field safety studies seen as highly important, as variability of age, sex, breed, husbandry may have impact
- **Challenges / complexity / expense of recruiting clinical patients**
  - Working through veterinary practices: with negative controls hardly acceptable in cases of infectious disease
  - Individually owned animals, trial conduct challenging
  - Alternative, where no model available

Laboratory studies as alternative

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- **Challenge studies**
  - Availability
  - Validity (strain etc.)
  - Ethics (3Rs etc.)
  - Cost

- **Use of lab animal models**
  - Availability
  - Validity
  - Ethics (3Rs)

AVC view

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- In many cases, field efficacy studies in pets may not generate results needed to assess the efficacy in pets
- Current requirements lead to increased costs, longer time to market and reduced availability of vaccines for certain diseases
- Current requirements for CA vaccine field efficacy studies are unsatisfactory because of above challenges
- Where laboratory efficacy studies are not entirely satisfactory: propose to improve them and replace current field efficacy studies
- Field safety studies are necessary to confirm product safety in relatively large number of animals representative of the population
- Field safety studies could be used to generate some data on markers of efficacy e.g. serology, cytokine response etc., but no clinically relevant effect should be required, where efficacy demonstrated under laboratory conditions for a vaccine.

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Thanks to the co-authors of this presentation:

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Thank you