Veterinary

Dossier requirements for EU – P4 Efficacy

Part 4 – Efficacy

DIRECTIVE(S)	
Regulation (EU) 2019/6	Annex II, Section IIIb - "*Requirements for Immunological veterinary medicinal products*", PART 4, EFFICACY
Ph. Eur. 0062	"*Vaccines for Veterinary Use*" – section 2-2-1
Ph. Eur. 5.2.7	"*Evaluation of efficacy of veterinary vaccines and immunosera*"
Ph. Eur. xxxx	Product-specific EP monograph

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EMA GUIDELINES	
EMEA/CVMP/552/02	*"Guideline on EU requirements for batches with maximum and minimum titre or batch potency for developmental safety and efficacy studies"*
EMA/CVMP/IWP/315887/2017	*"Guideline on the use of adjuvanted veterinary vaccines"*
EMEA/CVMP/004/04	*"Guideline on live recombinant vector vaccines for veterinary use"*
EMEA/CVMP/682/99	*"Duration of protection achieved by veterinary vaccines"*
EMA/CVMP/IWP/594618/2010	*"Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products"*
EMEA/CVMP/852/99	*"Note for guidance – Field trials with veterinary vaccines"*
EMA/CVMP/EWP/81976/2010	*"Statistical principles for veterinary clinical trials"*
EMA/CVMP/042/97-Rev1	*"Indications for veterinary vaccines"*
EMA/CVMP/IWP/439467/2007	*"Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals"*
EMA/CVMP/IWP/314550/2010	*"Guideline on the design of studies to evaluate the safety and efficacy of fish vaccines"*

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Chapters	Source information	Responsibility*
4.A. General requirements	Subject reports	R&D
B. Pre-clinical (lab) studies 1. – Onset of immunity/dose response 2. – Duration of immunity 3. – Effect of MDA 4. – Compatibility studies	Subject reports	R&D
C. Clinical trials (field studies) 1. – Field trial 1 2. – Field trial 2	Subject reports	R&D

**Task assigned to the function providing the documents/data.*
The overall responsibility for the writing and compilation of the dossier lies with Regulatory Affairs.

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About lab- and field studies……

EP 5.2.7- Evaluation of Efficacy of Veterinary Vaccines and Immunosera

"Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable";

EMA guideline on field studies, e.g.:

- Diseases where no experimental infection model exists
- Diseases where environmental factors play a role
- Certain diseases caused by more than one causal agent
- Involvement of special facilities (e.g. poultry drinking water vaccines, aqua vaccines)
- Scientific advise?

Regulation (EC) 2019/6

"When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required." - EMA guideline, early 2022

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Summary of Product Characteristics – Efficacy claims

TPP

Efficacy claim in the SPC:

For the active {*or passive*} immunization of chicken to:
- Prevent mortality, clinical signs and/or lesions of the disease/disease complex
- Prevent infection {*shown by re-isolation techniques*}
- Reduce mortality, clinical signs and/or lesions of the disease/disease complex
- Reduce infection {*shown by re-isolation techniques*}

Product-specific Immunogenicity test (EP)

Onset of Immunity: x days/weeks

Duration of immunity: x days/weeks {*MDV: life long*}

EP 5.2.7 - Evaluation of Efficacy of Veterinary Vaccines and Immunosera:
- *"Claims related to duration of immunity are supported by evidence of protection".*
- *"The test model described under Immunogenicity and/or Potency is not necessarily used to support claims regarding the duration of immunity afforded by a vaccine".*

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4.A. General requirements (i)

- Justification:
  - Choice of antigen strains (field/clinical relevance in EU)
  - Antigenic strength
    - Live vaccine: supported from min- and max titre (safety studies)
    - Inac vaccine: dose/response, validation potency test (potent/subpotent batches)

- Efficacy trials:
  - All results obtained, whether favourable or unfavourable, shall be reported
  - Test each target species by each method- and route of administration
  - Birds at minimum age (SPC)
  - OOI and DOI (unless justified e.g. MDV) is obligatory;
  - MDA+ studies needed when relevant from the vaccination program
  - Compatibility claims? e.g. HVT-ND-IBD and live Rispens

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4.A. General requirements (ii)

- Challenge:
  - Validation of the model (mimics natural route of infection)
  - Origin/source/strength/suitability of the challenge strain(s)
  - Heterologous challenge (unless justified)

- Methods used to evaluate efficacy parameters:
  - Validity
  - Validation

- Vaccine batches:
  - Representative of Part 2 of the dossier (explain and justify deviations)
  - Live vaccine contains antigens from MSV+5 or MSB+5
  - For multivalent vaccines, all studies are conducted with the full product and the largest combi

- Subject reports:
  - Minimum information as required from Annex II of Regulation (EC) 2019/6

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4.B. Laboratory trials

- Trials:
  - Well-controlled laboratory conditions (≠GLP)
  - Onset of immunity:
    - Challenge according to EP
    - Cross check with proposed SPC claims!
    - Include data on serology, if relevant for DOI/field studies
  - MDA+:
    - According to OOI
    - Challenge at age after MDA have disappeared (kinetics maternally antibodies)
  - Duration of immunity:
    - Challenge or serology?
    - Serology needs protective quantitative/qualitative link to the OOI challenge data.

- Animals:
  - OOI/DOI: SPF chicken
  - MDA+: commercial animals – provide evidence of MDA

- Vaccine batch(es):
  - R&D or GMP (check seed lineage!)
  - Minimum titre (live)
  - Minimum potency (inac)

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4.C. Field trials (i)

Liaise with national competent authority on local requirements!

- Combined safety and efficacy:
  - According to GCP
  - At least 2 different premises in EU (or elsewhere representing EU situation)
  - Double blinded (in case of subjective parameters), if possible

- Animals:
  - Not previously vaccinated with the same active substances
  - Report immunological status of animal groups prior to the start of the trial (i.e. historical vaccination with related products)
  - Use proper controls, or in case of herd vaccination, compare with other related EU registered product
  - (Most critical route of administration e.g. intranasal and method e.g. spray)
  - (Most relevant category of target species, at the minimum age)
  - If the live vaccine spreads, separate vaccinates from controls.

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4.C. Field trials (ii)

- Vaccine batch(es):
  - R&D or GMP (check with local requirements)
  - Live titre or potency according to routine production batch

- Parameters analyzed, e.g.:
  - Local reactions
  - Weekly mortality, morbidity, lesions, age at slaughter and weight, feed conversion ratio, laying performance and hatchability
  - Serological response (correlation of protection related to SPC claims) – or take animals back to the lab for challenge

Advise

Please cross-check the Target Dossier Profile on planned studies/data for

Quality,

Safety, and

Efficacy

With Regulatory Affairs