Field efficacy trials for vaccines for food-producing animals

Challenges faced by Industry

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Focus group meeting, 22 June 2017, EMA, London
• IFAH-Europe welcomes the focus group meeting (and the vet vaccine initiative)

• Field efficacy trials for vet vaccines for food-producing animals are demanding, long, costly, and unpredictable by nature

• They can be very useful to assess efficacy for some claims (i.e. production-related claims in swine, poultry, fish), or to further define « economic expectations »

• …But they do not always add value

• Occasionally, they have lead to (counter-productive) SPC statements

• Reconsidering the approach (in which situations to perform field efficacy trials) may have a positive impact on vaccine availability
Challenges faced by Industry when planning and running field efficacy trials are listed as follows:

- Timelines
- Field trial permit
- Field trial planning and design
- Field trial itself - Common findings
- Recent examples

IFAH-Europe proposes a possible way forward
Timelines...From plan to final report

- Significant!
  
  Up to 12-18 months timeline

- Direct impact on MA submission/approval timelines
  
  Field trials form the last part of the EU development programs
Field trial permit

- Process, extent and clarity of requirements vary per MS

  Potential impact on timelines

- Epidemiological/pathological changes may occur in the farm between field trial permit application and field trial permit approval

  Potential impact on trial suitability/validity
A lot of aspects to consider – Illustrates the challenges:

- Field safety and efficacy trial OR field efficacy?
  - May impact farm selection

- Vaccine titre/potency: minimum or standard?
  - Need to produce specific batch may impact timelines
  - Depending on design and results, may impact vaccine specifications
Field trial design & planning

- Which **primary criteria**? Which **secondary criteria**?

- Growing expectations to re-demonstrate all claims under field conditions
- Some « claims » especially challenging to demonstrate under field conditions (eg, reduction of shedding ?)
- Multi-valent vaccines : trials +++
- Multiple sub-category of target species (calves, breeding females, broilers, breeders, layers,…): trials +++
- Targeted pathogen(s) involved in multi-factorial diseases ? If so, how to assess efficacy in a robust manner ?
- Relevant strain differences (antigenic/genetic) ?
- Relevance of serology, where used ?
Field trial design & planning

• **Negative control** group:
  - Scientifically sound … But not representative of true field situation (worst case scenario)
  - Sometimes not allowed by the owner and/or unacceptable for animal welfare
  - Compensation for costs associated with negative controls can be very expensive
  - How to manage if live vaccine is shed/spread?

• **Positive control** group:
  - Non-inferiority trials can be difficult, especially in field conditions
  - How to ensure efficacy of the test vaccine is assessed/shown?
  - Is such design scientifically sound?
Field trial design & planning

- **Vaccination status** at the farm?
  - Do vaccination schedules need adjustments before and after the test vaccine inclusion? If so, may be difficult for the owner to accept
  - Historic use of live vaccines in the farm (especially for poultry)? May jeopardize the trial (presence of vaccinal strain previously used?)

- **Inclusion criteria**:
  - How realistic are they? Specific countries to be selected (and associated requirements)?
  - How to assess « disease history » and maximize probability of challenge exposure? Ultimately no guarantee

- **Practical aspects**
  - Specific clinical assays? Commercial kit validation?
  - Challenging to obtain good quality of data recording (inexperienced recorders)
  - Trainings needed to address GCP etc
Field trial design & planning

• **Statistics** :
  - Lack of predictability of infection pressure: Difficult to design appropriately-powered studies
  - Very large number of animals/Very large farms may be needed
  - Particular issue of live vaccines – How to ensure valid statistical comparisons, through adequate replication of experimental units, if treatment groups cannot be commingled?

• **Compensate for lack of predictability** ?
  - Vaccinate under field and challenge under lab (poultry/swine) ?
  - Is this really different from true laboratory challenge?
  - Not representative of field situations
  - Animal welfare issues
Field trial itself – Common findings

- **No or low challenge exposure**
  - Very frequent!
  - Impact of bio-safety measures
  - Numerical, but no statistically significant differences between groups

- **Pre-existing homogenous immunity**
  - Endemic diseases
  - Historic use of existing vaccines

- **Intercurrent infections**
  - Jeopardizes interpretation of results

- **Lack of « success reproducibility »** across multiple farms
Multiple recent examples of MA or variations (MRP/DCP or CP) where field efficacy trials did not bring added value (on SPC):

- Swine inactivated PCV2-M.Hyo
- Swine inactivated Parvo-Erysipelas
- Swine inactivated Leptospira
- Swine inactivated M. Hyo
- Swine live PRRSv
Recent examples

- Negative SPC statement, where no statistically significant differences were observed between vaccinates and controls, in presence of a low challenge exposure in the farm:

  "Efficacy was demonstrated under laboratory but not under field conditions »

- Expected to remain « forever » in the SPC even if good pharmacovigilance data, in absence of additional « successful » field efficacy trials

- Clear competitive disadvantage, and counter-productive

- Field study with GMO poultry vaccine was considered too contained and thus not representative for field
Conclusion & IFAH-Europe proposals

• Many challenges faced by Industry, at multiple levels
  • Especially, lack of predictability of (significant) field exposure is an issue
  • Controls are an issue (difficult to define how to manage them)
  • (multifactorial) nature of many diseases

• In many cases, field efficacy trials have not added any value (vs SPC)
• Absence of valid field challenge cannot be blamed on the vaccine
• Field efficacy trials should not be a “tick-box” exercise
• No field efficacy studies required for the US, but in the field vaccines perform similarly
• IFAH-Europe is not against field efficacy trials for vaccines
• IFAH-Europe favours field efficacy trials, where relevant for proposed claims
Conclusion & IFAH-Europe proposals

• Where efficacy is well-demonstrated under lab conditions & all SPC claims are supported & risk/benefit balance is positive:

  ✓ Field safety studies only

  ✓ No negative statement in the SPC, where no field efficacy trials are conducted in such scenarios

  ✓ Applicants may still include field efficacy trials in the MA application

• Where efficacy cannot be demonstrated under lab conditions, and/or where specific claims are desired:

  ✓ Field safety and efficacy studies
Conclusion & IFAH-Europe proposals

• **Positive impact** expected on:

  ✓ Vaccine development costs
  ✓ Freeing resources for research and development
  ✓ Number of vaccine development projects
  ✓ MA submission/Approval timelines
  ✓ ….And ultimately veterinary vaccines availability
IFAH-Europe proposals – decision tree

Is a challenge model available (with measurable parameters related to infection/disease)?

No

Yes

Do/can laboratory efficacy studies support all SPC claims, and are those claims sufficient to build a positive Risk/Benefit balance?

No

Yes

- No field efficacy trials are needed
- No negative statement in the SPC
- Applicants may still include field efficacy trials in the MA application

- Field efficacy trials are needed (for all or some claims)
Thank you

QUESTIONS?