Field efficacy trials for vaccines for food-producing animals

Challenges faced by Industry

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Introduction

- 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

Introduction

- **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

Field trial design & planning

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

Recent examples

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:

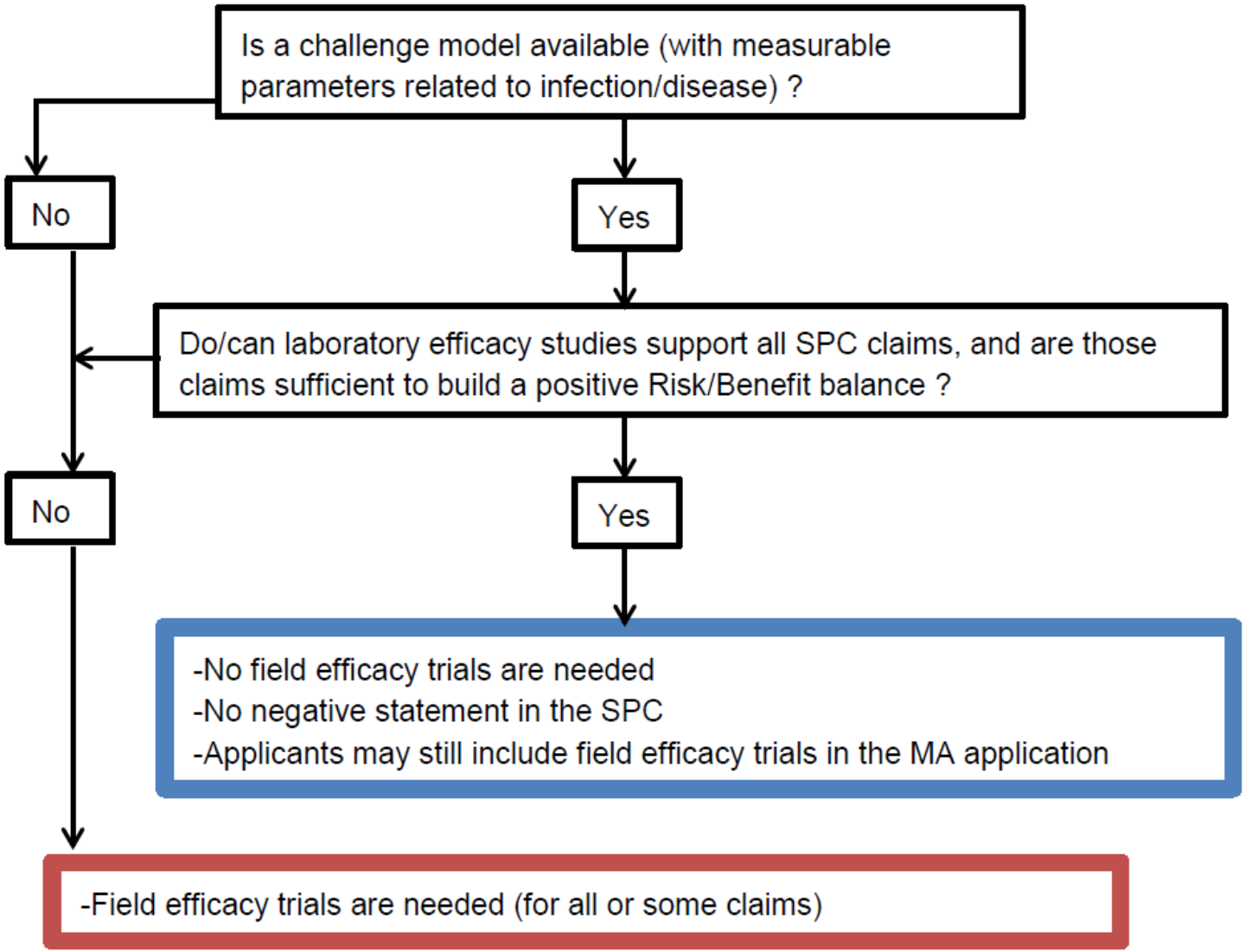
  - ✓ **Field safety and efficacy studies**

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



Thank you

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Representing the European Animal Health Industry

QUESTIONS ?