9 November 2017
EMA/405642/2017
Veterinary Medicines Division

Report on the Focus Group meeting with invited stakeholders on field efficacy trials in the context of an EU authorisation for veterinary vaccines

Executive summary

On 22 and 23 June 2017 a Joint European Medicines Agency (EMA)/Heads of Medicines Agencies (HMA) focus group meeting was held at the EMA bringing together regulators, industry and academic experts for exchanging views on specific challenges faced by industry in performing field trials to support efficacy claims for veterinary vaccines and on how these challenges might be overcome whilst still obtaining adequate assurances of the expected efficacy of a vaccine under field conditions. The objectives of the meeting were to identify specific challenges faced by industry in performing field trials to support efficacy claims, to identify the value that field efficacy data may bring to the dossier for marketing authorisation of a veterinary vaccine, to identify possible alternative sources of information on expected efficacy of a vaccine under field conditions and finally to make recommendations on the need for field efficacy trials to support efficacy claims. The role of field efficacy trials in the context of improving the availability of veterinary vaccines in the EU was identified by industry as one of their highest priorities during the 2015 Joint EMA/HMA workshop on requirements for the authorisation of veterinary vaccines in the EU.

Industry made the case that the requirement for efficacy field trials poses a significant challenge for bringing new vaccines to the market given their high costs, seasonality of challenge, delays in receiving trial permission for using GMO or live products and the difficulties in ensuring appropriate/adequate challenge that often lead to inconclusive results and render the data of lesser value for determining the efficacy of the product, while not necessarily adding value to the efficacy assessment. It was recognised that although EU legislation provides an exemption from the requirement to carry out field efficacy trials it would be useful to define those situations in which a justification for not providing field trials will be accepted by the regulatory authorities. It was also agreed that when there is an acceptable justification for not providing data from field efficacy trials, negative statements in the SPC should not generally be included. Regulatory authorities are of the opinion however that for reasons of fairness and transparency the SPC needs to reflect if field data have been provided, and consideration on how best to express this in the SPC, will be required. The following situations were recognised with regards to the need of field efficacy trials: (i) those for which field trials are always required (e.g. certain production-related claims or those diseases for which no

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

laboratory model exists) (ii) those for which an exemption may be accepted if justified and, (iii) those for which an exemption will always be accepted (e.g. well established challenge models such as canine distemper, epizootic diseases that are exotic to the EU and where vaccination is prohibited as part of control policy). Defining criteria that would be consistently applied by regulators in reaching a decision on whether or not field trials would be required would therefore be helpful. Such criteria could include the disease, species, indication/claim, type of vaccine, etc. Some participants considered that it would also be beneficial to produce lists of diseases for which field trials would or would not be required. However others were concerned that it would be complex and resource intensive to attempt establishing lists in advance of an actual application. CVMP would need to reflect on the possibility of creating and publishing a list of diseases for which field trials would not be required. Further consideration is therefore required by regulators as to how best to provide the necessary predictability to applicants. Preliminary data presented by EMA from veterinary vaccines authorised via the centralised procedure and the respective role of field efficacy data were discussed and there was agreement that further analysis would be useful. Possible alternative sources of information in support of efficacy that can reduce the risk of uncertainty for regulators in the absence of field data where discussed; epidemiological modelling in certain situations, and meta-analysis of literature data were considered useful. Passive pharmacovigilance data however were considered to be of limited value in this context. Finally a benefit in to engaging further with academia with regards to how best to generate data on efficacy of veterinary vaccines was recognised by a number of participants.

Background and approach

On 22 and 23 June 2017 a Joint European Medicines Agency (EMA)/Heads of Medicines Agencies (HMA) focus group (FG) meeting was held at the EMA bringing together regulators, industry and academic experts for exchanging views on scientific, regulatory and technical challenges faced by industry in performing field trials in the EU to support efficacy claims for veterinary vaccines. The meeting explored how these challenges might be overcome whilst still obtaining adequate assurances of the expected efficacy of a vaccine under field conditions. The objectives of the FG meeting were to:

- identify specific challenges faced by industry in performing field trials to support efficacy claims,
- identify the value that field efficacy data may bring to the dossier for marketing authorisation of a veterinary vaccine,
- identify possible alternative sources of information on expected efficacy of a vaccine under field conditions,
- make recommendations on the need for field efficacy trials to support efficacy claims.

The need for this meeting was identified by the Joint EMA/HMA Steering Group on veterinary vaccine availability on the basis of their assessment of the analysis provided by IFAH-Europe on challenges faced by veterinary vaccines industry during the Joint HMA/EMA Workshop on requirements for the authorisation of veterinary vaccines in the EU that was held in 2015. The proposal for the focus group meeting was endorsed by both CVMP and HMA as the highest priority for vaccine availability in 2017 and was included in the work programmes for both CVMP and IWP.

The meeting was divided into four sessions with each session corresponding to one of the meeting's objectives. Short presentations were given by speakers representing industry, regulatory authorities (EU and USA) and academic experts from the areas of epidemiology, infectious diseases, statistics and clinical trials. After the presentations participants debated the main issues around each objective and a summary of key findings from the discussion was presented by the Chair at the end of each session.

The meeting closed with the fourth session where the main conclusions of the meeting were agreed and a number of key points for consideration and follow-up by the Joint EMA/HMA Steering Group were made. The presentations given during the focus group meeting are available on the EMA website.

Discussion and conclusions

Session 1: Identify specific challenges faced by industry in performing field trials to support efficacy claims

A discussion on challenges faced by industry in performing field efficacy trials and their merits took place. Council Directive 2009/9/EC states that: "unless justified, the results from laboratory trials shall be supplemented with data from field trials". There is therefore an expectation in EU legislation that data from field trials will generally be supplied unless a suitable justification is provided. However, industry expressed the view that in practice field efficacy trials are routinely required by EU regulators to support an MA application and that justifications for not providing such trials may not be accepted. Industry expressed concern that this approach has a negative impact on availability.

Efficacy field trials are now routinely included in new vaccine development plans by industry to minimise the risk of delay to the corresponding Marketing Authorisation procedure that may arise due to the regulatory authority not accepting a justification for their omission and requesting such data during the procedure. In addition, Industry raised a concern that regulators increasingly require that negative statements advising of the absence of confirmatory field data are included in the SPC when such data are not available. Industry made the case that field trials to evaluate efficacy are a significant challenge for vaccine developers because of their high cost, complexity of design, and especially the uncertainty of outcome (Industry showed some examples where field efficacy trials did not yield confirmatory efficacy data, for example, due to absence of field challenge). Field efficacy trials may also be very long (typically, when production-related claims are assessed in food-producing animals) or difficult to plan (individual pet animals are not or cannot be exposed to disease). As a result, the requirement for field efficacy data can have a significant impact on the time for the product to reach the market, while not necessarily adding value to the efficacy assessment. Further, factors such as the seasonality of the field challenge and the process for obtaining permission to conduct a clinical trial (in particular for using GMOs or live products) could add many months to the study timeline. Given the challenges faced, Industry argued that there is a need for predictability in the way in which the exception from the requirement for field efficacy trials can be applied by regulatory authorities.

There was general agreement that vaccine indications as reflected in the SPCs have become more complex and specific in recent years. In addition negative statements were included when confirmatory field data are not available. Regulatory authorities were of the opinion, however, that for reasons of fairness and transparency the indication should accurately (precisely) reflect the efficacy data provided and the source of the data on which it is based (e.g. laboratory data only) but the intention was not for the indication to be viewed in a negative way. It was suggested that further consideration of the approach to drafting indications is warranted, in particular to consider the level of detail that is helpful or useful for the end user and whether the current drive to include more specific statements adds value.

The elements defining a successful challenge model and the conditions under which laboratory models can be considered representative of field conditions to support the claims of veterinary vaccines were discussed. It was highlighted that laboratory experiments may be difficult to design to reflect complex

field situations. Critical parameters for success identified were: the choice of the challenge strain (must be representative of epidemiological situation and produce measurable effects), the target animals (age, density and size of herds) and the reproducibility of the disease model. Meta-analysis of existing literature data, epidemiological modelling and the possibility of monitoring and reporting on efficacy in a more systematic manner post authorisation were proposed as possible alternatives to supplying field efficacy trial data in support of laboratory results.

Session 2: Identify the value that field efficacy data may bring to the dossier for marketing authorisation of a veterinary vaccine

In terms of the added value that field efficacy data brings to the dossier of a veterinary vaccine, there were mixed views. Some expressed also the view that there is not enough alignment in the understanding of vaccine efficacy versus vaccine effectiveness, with the latter being considered more relevant to the behaviour of the vaccine when deployed in the field.

Preliminary data from a review of immunological products authorised via the centralised authorisation procedure were presented. The findings suggest that, for some vaccines, field efficacy trials were pivotal in defining some indications and, in addition, field studies may provide data that increases understanding of the appropriate use of a vaccine and informs other sections of the SPC. However, for the majority of immunological products considered in the review, field data appeared to be of limited value from an efficacy perspective and was only generally supportive to the claims. Given the preliminary nature of the findings, it was generally agreed that further analysis of this dataset was necessary in order to provide more conclusive results. Some regulators underlined an unquantifiable element in terms of the increased confidence that field data provided to the benefit /risk assessment when considering vaccine claims that may not be obvious in this type of objective analysis.

The approach of the US regulator (USDA) to vaccine authorisation was also discussed. It was noted that although field safety studies are always required –-, vaccine efficacy is based on the results of laboratory studies supporting a simplified (single tier) label claim approach (that is, typically field efficacy studies are not required). It was stated that speed to market is important and that, once marketed, product users would determine conditions of use that are appropriate for their specific situation. Certain users of vaccines, particularly large integrated companies, are known to conduct their own evaluation of authorised vaccines under their own conditions of use. No evidence so far indicates a need to revise the USDA approach.

It was agreed that in order to provide predictability to applicants it would be useful to define, in advance, those situations in which a justification for not providing field trials will be accepted by the regulatory authorities. There was further agreement that for some diseases for which there are well established challenge and study design models, field trials do not play a critical role and are therefore not considered essential (e.g. rabies, distemper, canine parvovirus, swine parvovirus, etc.). On the other hand, it was considered that field trials would be important to justify certain claims relevant to production such as reduced weight losses, etc. In summary, the following situations were recognised: (i) those applications for which field trials are always required (e.g. most production-related claims or those diseases for which no laboratory model exists) (ii) those applications for which an exemption may be accepted if justified and, (iii) those applications for which an exemption will always be accepted (e.g. well established challenge model such as canine distemper, epizootic diseases that are exotic to the EU and where vaccination is prohibited as part of control policy).

There was discussion as to whether establishing a list of diseases for which field trials would not be required would serve as a good way forward or whether simply defining the criteria to be used to

identify such diseases would suffice. It was agreed that such a list would provide increased predictability for Industry, fairness (harmonised approach by regulators) and transparency. However, it was also acknowledged that it would not be very useful for emerging diseases. While Industry appeared supportive of the proposal to establish a list, further reflection by regulators was considered important, especially as it was recognised that it may be a complex and resource intensive exercise to create such a list in advance of receipt of information related to a particular product and the proposed indications (normally contained in a MAA dossier).

Session 3: Identify possible alternative sources of information on expected efficacy of a vaccine under field conditions

Speakers highlighted the potential of epidemiological modelling to upscale laboratory efficacy data to population level and to provide a greater understanding of the meaning of experimental data beyond simple statistical analysis from vaccine trials. A number of participants highlighted the importance of identifying the transmission rates as part of the efficacy of vaccines against infectious diseases and the possibility to study this through epidemiological modelling rather than small scale field trials. However, there was an acknowledgement that transmission rates may be difficult to demonstrate and that such modelling is possibly most relevant to the use of vaccines in eradication programmes. Examples were given of new vaccines both from the EU (e.g. vaccine against Bluetongue virus) but also from developing countries where epidemiological modelling expedited their authorisation and allowed their timely and successful use against endemic diseases. The challenges of conducting informative field efficacy trials were further discussed including: the large number of animals required in order to demonstrate significant impact of vaccination; the unpredictability of natural challenge that may be too low (fail to demonstrate an effect of vaccine) or may occur in association with other infectious agents (complicate result interpretation); and, the lack of information on transmission rates. However, it was recognised that field trials provide assurance to regulators that the protection observed under laboratory conditions also occurs under field conditions. It was highlighted that, where possible and practical, well designed and well populated field trials provide some of the best proof that a vaccine is able to perform under actual conditions of use in line with the claims for the product as specified in the SPC. On the other hand, small scale field trials may be unable to detect beneficial effects of vaccination, particularly at the population level. It is also recognised that poorly designed or poorly conducted field trials can provide a false level of assurance of the effectiveness of a vaccine.

The possibility of omitting field efficacy data in some situations and authorising a vaccine with a commitment to provide additional field efficacy data post authorisation was discussed. Industry expressed concern with the idea of moving to a system of post authorisation commitments for providing field efficacy trials.

It was recognised that passive pharmacovigilance data as currently produced may not be appropriate for use in assessing the effectiveness of vaccination, given the lack of structure (as an efficacy dataset), under-reporting and lack of focus on efficacy parameters.

Potential alternative approaches to supporting the efficacy of a product that were discussed included: epidemiological modelling where appropriate, proactive post authorisation reporting of efficacy and meta-analysis of literature data. The possibility to use risk management plans provided for under current EU legislation and routinely applied for the authorisation of human medicines was also considered as an option to reduce risk in absence of field efficacy data for veterinary vaccines.

On the issue of risk, it was suggested that there was a need for risk sharing between regulators and applicants when balancing the risks of not including field data against the benefits in terms of

increased availability/reduced time to market and ultimately the benefits for public/animal health. It was pointed out that applicants can already increase predictability by seeking scientific advice on whether or not field efficacy trials should be submitted as part of a dossier. Finally, some participants expressed the view that there may be benefits from engaging further with academia on how to generate data on efficacy of veterinary vaccines either through field trials or alternative approaches and how best to use this information in the authorisation procedure for the benefit of animal and public health.

Session 4: Make recommendations on the need for field efficacy trials to support efficacy claims

Session four engaged participants in discussions on the conclusions that could be drawn from the previous sessions and on how best to reflect them in the form of recommendations to those responsible for effecting change. The meeting identified several opportunities to be considered and concluded with the following key points:

1. Where it is possible and practical to carry out field efficacy trials to a sufficiently high standard they represent the highest level of proof that a vaccine is able to perform under practical conditions of use in line with the claims for the product as specified in the SPC. However, it was acknowledged that, for some vaccines, it is possible to have adequate proof of efficacy in the absence of field efficacy data.

2. EU legislation provides an exemption from the requirement to carry out field trials where this can be justified. In order to provide predictability to applicants it would be useful to define in advance those situations in which a justification for not providing field trials will be accepted by the regulatory authorities.

3. In principle, currently three situations were recognised: (i) those applications for which field trials are always required (e.g. certain production claims or for those diseases for which no suitable laboratory model exists) (ii) those applications for which an exemption may be accepted if justified and, (iii) those applications for which an exemption will always be accepted (e.g. well established challenge model such as canine distemper, epizootic diseases that are exotic to the EU and where vaccination is prohibited as part of EU control policy).

4. The current situation could be improved by defining criteria that would be consistently applied by regulators in reaching a decision on whether or not field trials would be required in support of a particular application. Such criteria could include the disease, animal species, indication/claim, type of vaccine (live, inactivated, method of administration), and the reliability and applicability of the laboratory model(s) (see (6), below).

5. Some participants considered that there would be benefit in producing a list(s) of diseases and/or indications for which field trials would or would not be required. However others were concerned that it would be complex and resource intensive to attempt establishing and maintaining lists in advance of an actual application.
   CVMP would need to reflect on the possibility of creating and publishing lists of diseases for which field trials would, or would not, be required.

6. For some diseases for which well-established challenge and study design models are available, field efficacy trials do not provide significant added value and their omission can be justified. Specific criteria to decide the diseases for which such exclusion can be applicable in the context of a veterinary vaccine application for an EU authorisation should be considered by experts. Possible parameters that can be considered may include: a) the availability of a challenge model with reproducible signs of the disease, b) a challenge model including a strain representative of the EU epidemiological situation, c) a challenge able to produce clinical signs for which a good scoring system exists, d) where relevant, a challenge pathogen that can be excreted and measured using well established and validated methods, e) a study design in which the vaccine can be administered by the intended route and with animals representative of the target population expected in field conditions.

7. When there is an acceptable justification for not providing data from field efficacy trials or when data from field efficacy trials do not provide conclusive evidence, negative statements in the SPC should not generally be included. Regulatory authorities are of the opinion however that for reasons of fairness and transparency the SPC needs to reflect if field data have been provided, and consideration on how best to express this in the SPC will be required.

8. Completing the analysis of the preliminary data presented by EMA from veterinary vaccines authorised through the centralised procedure and the respective role of field efficacy data was considered useful in order to reach conclusions that can potentially assist with establishing either specific criteria by which omission of field efficacy data can be justified in the context of a veterinary vaccine application for an EU authorisation and/or a list of diseases for which efficacy trials are required, or not.

9. Field trials provide assurance to regulators that the protection observed under laboratory conditions also occurs under field conditions. It was noted that poorly designed or poorly conducted field trials can provide a false level of assurance and, conversely, that small scale field trials may be unable to detect beneficial effects of vaccination, particularly at the population level. Alternative sources of information that can support efficacy and reduce the risk of uncertainty in the absence of field data should therefore be accepted by regulators. Such sources could include evidence of vaccine 'take' (for example, serological marker of response to vaccination, where a correlation with efficacy has been established), epidemiological modelling in certain situations, and meta-analysis of literature data.

10. The possibility of omitting field data in some situations and authorising a vaccine with a minimum level of pre-authorisation data with a commitment to provide additional field efficacy data post authorisation was discussed. However, the limitations of the current system of passive pharmacovigilance to detect suspected lack of efficacy were recognised and industry were not in favour of moving to a system of post authorisation commitments for providing field efficacy trials.

11. There is a benefit in engaging further with academia with regards how best to generate data on efficacy of veterinary vaccines (either through field efficacy trials or alternative approaches) and how best to use this information in the authorisation procedure for the benefit of animal and public health.

12. Part of the challenge faced by applicants relates to the different expectations that exist between assessors across the Network in terms of when field efficacy trials are, and are not, required. In addition to clarifying when exceptions should apply, attention should therefore be given to training to promote consistency of understanding of field efficacy trials and alternative sources of assurance.

Next steps

This report, including the above points, considerations and suggestions made during the focus group meeting will be made publically available following appropriate consultation. The joint EMA/HMA Steering Group on veterinary vaccine availability will consider the findings of the final report and will decide on the appropriate follow up, particularly in terms of making specific recommendations to those that are responsible for the assessment and authorisation of veterinary vaccines in the EU.

Disclaimer

The views expressed in this report are the views of the participating experts and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its Committees or working parties.

Annex

Programme - Focus group with invited stakeholders on field efficacy trials in the context of an EU authorisation for veterinary vaccines

Thursday, 22 June 2017, 13:00 – 18:00
Friday, 23 June 2017, 9:00 – 13:30

Day 1, Thursday 22 June 2017 from 13:00 to 18:00 (Room 03-E)

Programme	Speaker	Time
OPENING SESSION		
– *Welcome remarks*	Dr Fia Westerholm (EMA)	13.00 – 13.05
– *Setting the scene: Steering Group introduction to focus group and objectives*	Dr Jean-Pierre Orand (HMA)/ Dr Faye Ioannou (EMA)	13.05 – 13.15
SESSION 1: Identify specific challenges faced by industry in performing field trials to support efficacy claims **Chair: Esther Werner (EU regulator)**		
– *Challenges faced by industry in performing field trials to support efficacy claims for food producing species*	Dr Frederic Descamps (IFAH- Europe)	13.15 – 13.30
– *Challenges faced by industry in performing field trials to support efficacy claims for small animals*	Dr Klaus Hellman (AVC)	13.30 – 13.45
– *Challenge models: under which conditions can the laboratory models be representative of field conditions to support the claims of veterinary vaccines - what are the pivotal parameters for defining the success of a challenge model*	Prof Etienne Thiry (University of Liège)	13.45 - 13.55
Moderated plenary discussion	All	13.55 – 15.10
Conclusions on session 1	All	15.10 – 15.25
COFFEE BREAK (15.25 – 15.45)		

Programme	Speaker	Time
SESSION 2: Identify the value that field efficacy data may bring to the dossier for marketing authorisation of a veterinary vaccine **Chair: Dr Jacques Léchenet (Industry representative)**		
– *EU Regulatory perspective and thoughts on field efficacy data*	Dr Jean-Claude Rouby (CADVVA, CVMP, ANSES)	15.45 – 16.05
– *Summary of interim results from analysis of field efficacy data for centrally authorised products*	Dr Martin Ilott (EMA)	16.05 – 16.15
– *Requirements for field efficacy trials for the authorisation of veterinary vaccines in the USA and the rationale behind them*	Dr Paul Hauer (USDA - Centre for Veterinary Biologics)	16.15 – 16.30
Moderated plenary discussion	All	16.30 – 17.30
Conclusions on session 2	All	17.30 – 18.00

Day 2, Friday 23 June 2017 from 9:00 to 13:30 (Room 03-E)

Item Agenda	Speaker	Time
SESSION 3: Identify possible alternative sources of information on expected efficacy of a vaccine under field conditions **Chair: Prof Kris De Clercq (Academic expert)**		
– *Obtaining information on field efficacy for veterinary vaccines- challenges and solutions from an epidemiological perspective)*	Prof James Wood (Cambridge University)	09.00 – 09.15
– *Alternative sources provided by recent system modelling in animal health for the upscaling of vaccine efficacy to the population level*	Dr Hans-Hermann Thulke (Helmholtz Centre for Environmental Research)	09.15 – 09.30
Moderated plenary discussion	All	09.30 – 10.45
Conclusions on session 3	All	10.45 – 11.00
COFFEE BREAK (11.00 – 11.30)		

Item	Agenda	Speaker	Time
SESSION 4: Make recommendations on the need for field efficacy trials to support efficacy claims **Chair: Dr David Murphy (CVMP Chair)**			
	Presentation of conclusions on session 1 and 2	Chairs	11.30 – 11.50
	Moderated plenary discussion	All	11.50 – 13.15
	Conclusions on session 4	All	13.15 – 13.30

List of speakers

Dr Jean-Pierre Orand (Head of ANMV – French Agency for Veterinary Medicines)

Dr Faye Ioannou (European Medicines Agency - Veterinary Medicines Division)

Dr Frederic Descamps (IFAH- Europe)

Dr Klaus Hellmann (Association of Veterinary Consultants - AVC)

Professor Etienne Thiry (University of Liège)

Dr Jean-Claude Rouby (CADVVA, CVMP, ANSES)

Dr Martin Ilott (European Medicines Agency - Veterinary Medicines Division)

Dr Paul Hauer (USDA-Center for Veterinary Biologics)

Professor James Wood (University of Cambridge)

Dr Hans Thulke (Helmholtz Centre for Environmental Research-Leipzig)

Session chairs

Session 1 - Dr Esther Werner

Session 2 - Dr Jacques Léchenet

Session 3 - Professor Kris De Clercq

Session 4 - Dr David Murphy