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EMA/CVMP/IWP/309514/2015
Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper on guidance on statistical principles for clinical trials for immunological veterinary medicinal products

Agreed by Immunologicals Working Party (IWP)	October 2015
Adopted by CVMP for release for consultation	10 December 2015
Start of public consultation	18 December 2015
End of consultation (deadline for comments)	31 March 2016

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1. Introduction

A guideline on statistical principles for veterinary clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010) was adopted in 2012. This guideline provides guidance on the statistical principles to be considered in the design, conduct, analysis and evaluation of clinical trials to demonstrate efficacy and/or safety of an investigational veterinary pharmaceutical product in animals.

The safety and efficacy of immunological veterinary medicinal products (IVMPs) are investigated in suitably designed laboratory and field studies in accordance with European Pharmacopoeia (Ph. Eur.) chapters 5.2.6 *Evaluation of safety of veterinary vaccines and immunosera* and 5.2.7. *Evaluation of efficacy of veterinary vaccines and immunosera*, and where applicable, specific Ph. Eur. monographs. Demonstration of safety and efficacy for IVMPs differs from pharmaceutical products in the sense that pivotal data is generally generated in laboratory scale studies and the major objective of large scale field trials is to supplement and support the observations from the laboratory studies. Therefore while the statistical principles outlined in EMA/CVMP/EWP/81976/2010 are relevant, the evaluation of efficacy and safety for IVMPs is focused on the outcome of small scale trials where the interpretation of data may need special consideration due to the uncertainties associated with limited data sets.

2. Problem statement

The guideline on statistical principles for veterinary clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010) provides guidance on the design and analysis of clinical trials. Much of this guidance is focussed on methods used for large scale trials used to demonstrate safety and efficacy for pharmaceutical products. The general use of small scale laboratory studies to demonstrate efficacy for IVMPs requires special consideration during interpretation of data due to the inherent uncertainty associated with limited data sets.

3. Discussion (on the problem statement)

Study design requirements for efficacy and safety evaluation differ between IVMPs and pharmaceutical products. Primarily small scale experimental studies are used to demonstrate both safety and efficacy for IVMPs. Safety studies are carried out in accordance with VICH GL44 and Ph. Eur. chapter 5.2.6, typically using groups of eight animals. Efficacy is also usually demonstrated in small scale studies by comparing infection rates in groups of vaccinated and non-vaccinated animals exposed to virulent challenge organisms. Where numbers of animals are specified in Ph. Eur. monographs these are usually restricted to the minimum number expected to be needed to demonstrate an effect and compliance criteria are often specified.

Large scale field trials are most commonly used to support and supplement the observations from the laboratory studies under field conditions and on a large scale rather than to provide primary safety and efficacy data. However in certain cases, field trials may be used to investigate efficacy parameters that it is not possible to study under laboratory conditions such as diseases where a suitable experimental infection model does not exist, certain diseases caused by more than one causal agent, cases where special husbandry facilities are involved, and diseases where environmental factors play a major role in the aetiology.

The statistical principles described in the guideline on statistical principles for veterinary clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010) are relevant also for IVMPs. However, the type of studies generally used for demonstration of safety and efficacy differ

and laboratory scale studies are used to a greater extent as compared to pharmaceuticals. Data from limited data sets are associated with a higher degree of uncertainty and consequently the relevant use of statistical principles and the interpretation of data require special consideration. It will therefore be valuable to provide guidance on how to make appropriate statistical evaluation and interpret data from the small scale studies commonly used for IVMPs.

4. Recommendation

The Immunologicals Working Party (IWP) recommends drafting guidance on appropriate statistical evaluation and interpretation of data from clinical trials for IVMPs. Although the basic statistical principles are the same irrespectively of product, the greater emphasis on small scale studies used for IVMPs entails a somewhat different approach than those used for pharmaceutical products. Revised guidance is therefore needed to address this difference in approach. This could be presented as an annex to the existing guideline on statistical principles for veterinary clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010), or as a stand-alone document.

5. Proposed timetable

December 2015	Concept paper released for consultation
March 2016	Deadline for comments
Q4 2016	Proposed date for release of draft guideline for consultation
Q1 2017	Deadline for comments
Q3-4Q 2017	Expected date for adoption by Committee

6. Resource requirements for preparation

Drafting the guideline will involve one rapporteur and one co-rapporteur.

Preparation of the draft guideline will require discussion at 2 – 3 IWP meetings.

7. Impact assessment (anticipated)

It is anticipated that the guidance would benefit both industry and regulators due to clarification regarding the use of statistical principles and interpretation of data from clinical trials for IVMPs.

8. Interested parties

Veterinary pharmaceutical industry and consultants

Regulatory authorities, in particular statisticians

Efficacy Working Party

Scientific personnel involved in the conduct of clinical trials for IVMPs

9. References to literature, guidelines, etc.

European Pharmacopoeia, European Directorate for the Quality of Medicines & HealthCare (EDQM), Strasbourg.

VICH Guideline 44: Target animal safety for veterinary live and inactivated vaccines.

Guideline on statistical principles for veterinary clinical trials for veterinary medicinal products (pharmaceuticals), EMA/CVMP/EWP/81976/2010.

Note for guidance: Field trials for veterinary vaccines, EMEA/CVMP/852/99.