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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

CONCEPT PAPER ON THE REVISION OF THE GUIDELINE ON STATISTICAL PRINCIPLES FOR VETERINARY CLINICAL TRIALS (EMEA/CVMP/816/00)

AGREED BY EFFICACY WORKING PARTY (EWP-V)	May 2009
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	17 June 2009
END OF CONSULTATION	30 September 2009

The proposed guideline will replace the current "Guideline on Statistical Principles for Veterinary Clinical Trials (EMEA/CVMP/816/00)".

Comments should be provided using this template to vet-guidelines@emea.europa.eu
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KEYWORDS	Guideline, veterinary medicine, statistics, clinical trial

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1. INTRODUCTION

The guideline on statistical principles for veterinary clinical trials was adopted in June 2002. Since then it has been referred to extensively in full application dossiers including clinical trials in the target species, mainly clinical field studies. The guideline is basically similar to its counterpart in human medicine (Note for Guidance on Statistical Principles for Clinical Trials, CPMP/ICH/363/96) and addresses, in addition, specific veterinary issues.

2. PROBLEM STATEMENT

The guideline on statistical principles for veterinary clinical trials was prepared in the late 1990s and came into effect in June 2002. The guideline is extensively used for full application dossiers including clinical trials in the target species. Since then considerable experience has been gained and a number of issues relating to hypothesis testing (superiority, non-inferiority), confidence intervals for response variables, power calculations and other statistical methods have been identified by regulators that would need more clear guidance and have been brought to the attention of the CVMP-Efficacy Working Party.

3. DISCUSSION (on the problem statement)

Based on increased general experience regarding statistical evaluation of veterinary clinical studies a number of issues have been identified that could benefit from the provision of more information in the guideline text.

The major issues for discussion are as follows:

Section 2.2.2 Specific issues related to the use of rating scales (content validity, intra- and inter-rater validity, responsiveness for detecting differences) should be addressed in detail.

Section 2.3 More detailed information on the different types of bias (e.g. selection) that might occur within statistical analyses should be given, and methods to avoid such bias as far as possible should be described.

Section 3.3.1 More information in relation to hypothesis testing is deemed necessary, in particular specific information on the appropriate use of superiority, equivalence and non-inferiority testing In particular, information on the possibility for switching between equivalence and non-inferiority testing should be provided.

Section 3.3.2 Non inferiority is one of the hypotheses most used by applicants and requires clearer guidance on the choice and justification of non-inferiority margins; also, internal validity of the study should be emphasized as a pre-requisite for obtaining meaningful results; that means the study should be designed and conducted in a way to demonstrate a recognized level of efficacy of the comparator product.

An upper bound of at most 5% for the type I error should be fixed for equivalence and non-inferiority trials as this is the risk of authorizing a non-efficacious product.

The inappropriateness of difference tests for proving equivalence or non-inferiority should be clearly addressed by giving a summary about type I and II errors, statistical power and the associated risks.

Section 4.3 The chapter on interim analyses should be reviewed to provide further guidance on how to conduct them. It should be specified that as a rule the use of interim analyses should be avoided and will only be accepted when clearly justified.

Section 5.1.1 More guidance should be included on sample size calculations including the method and assumptions in relation to variability, power and significance level

Section 5.2	The notion of "Full Analysis Set" (as defined in the Human Guidance) should be introduced, and its importance in equivalence and non-inferiority trials should be noted. Further clarification should be given on the reporting of the flow of participants through the trial and of the roles of different analysis sets (e.g. ITT, PP) in different study designs e.g. superiority, non -inferiority.
Section 5.5.3	More guidance on when to use one- or two-sided tests for significance is deemed necessary; in addition, the need of statistical power calculations in relation to p-values should be addressed in more detail; The impact of multiple testing on the reliability of p-values should be provided, i.e. more information on adjustment of p-values in relation to multiplicity testing.
Section 5.7.4.	If claims are based on the findings for subgroups, the prerequisites for this should be clarified. Guidance should also be given on use of interaction tests for subgroup analysis.
Section 7	Include recommendation to provide graphical demonstration of statistics in addition to tables.
New section	Include guidance on meta-analytic techniques which in some cases may be a useful tool to summarise overall efficacy results or to analyse less frequent outcomes of the overall safety evaluation, if appropriate. A correct data collection and data validation is vital for a statistical analysis and clinically meaningful outcome; more guidance should be included on this. Include guidance on survival analyses in particular in situations if a long-term treatment is intended and a substantial proportion of treatment withdrawals or deaths are expected.

4. RECOMMENDATION

The CVMP recommends revising the current guideline to consider the above mentioned issues.

5. PROPOSED TIMETABLE

June 2009	Concept paper adopted by CVMP for release for consultation
30 September 2009	Deadline for comments from Interested Parties
3Q 2010	Expected date for adoption of the revised guideline by EWP
3-4 Q 2010	Draft guideline for discussion and adoption by CVMP for release for consultation

6. RESOURCE REQUIREMENTS FOR PREPARATION

Preparation of the revision would involve one rapporteur assisted by two co-rapporteurs.

Preparation of the draft guideline will require discussions at 2 – 3 EWP meetings.

7. IMPACT ASSESSMENT (Anticipate)

The anticipated benefit for both industry and regulators is due to clarification regarding statistical requirements for veterinary clinical studies.

8. INTERESTED PARTIES

Veterinary pharmaceutical industry and consultants

Regulatory authorities, in particular statisticians

Scientific personnel involved in the conduct of veterinary clinical trials