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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

GUIDELINE FOR THE DEMONSTRATION OF EFFICACY FOR VETERINARY MEDICINAL PRODUCTS CONTAINING ANTIMICROBIAL SUBSTANCES

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GUIDELINE FOR THE DEMONSTRATION OF EFFICACY FOR VETERINARY MEDICINAL PRODUCTS CONTAINING ANTIMICROBIAL SUBSTANCES

1. INTRODUCTION

This guideline replaces the previous guidance note (III/3778/90) in Volume 7A. It should be read in conjunction with the *Guideline on pre-authorisation studies to assess the potential for resistance resulting from the use of antimicrobial veterinary medicinal products* (EMEA/CVMP/244/01-FINAL-corr).

It applies to antimicrobial substances for all routes of administration and to all pharmaceutical forms except for antimicrobials intended for intramammary administration, for which only section 2, Pharmacodynamics applies. For the conduct of efficacy studies on intramammary products please see *Guidelines for the Conduct of Efficacy Studies for Intramammary Products for Use in Cattle* (EMEA/CVMP/344/99).

This guideline applies to all new applications for Marketing Authorisation for veterinary medicinal products containing new antimicrobial substances or antimicrobial substances contained in veterinary products already authorised [1].

The objective of this guideline is to specify the data required to demonstrate the therapeutic efficacy of an antimicrobial substance for a given indication(s) using a therapeutic regimen that aims to minimise the risk of selecting antimicrobial resistant bacteria. Thus, the following sections give guidance on the essential topics which the applicant should cover in the description of efficacy, i.e. pharmacodynamics, pharmacokinetics and clinical trials and, in addition, on the detection of development of antimicrobial resistance.

2. PHARMACOLOGY

Pharmacokinetic and pharmacodynamic studies uniquely contribute to describing, justifying, and optimising the therapeutic regimen.

Any pharmacodynamic or pharmacokinetic interaction with other substances should be documented and discussed in relation to its clinical significance or potential impact on resistance.

Studies on pharmacodynamics should be performed according to validated and internationally accepted methods. Studies should be conducted according to the principles of Good Laboratory Practice (GLP) (see Council Directive 88/320/EEC as amended).
Studies on the pharmacodynamic effects and mode of action, which form the basis for the use of the active substance, should be provided. Other effects of the active substance should also be documented.

For the conduct of pharmacokinetic studies please see the Guideline «*Conduct of Pharmacokinetic studies in target animal species »* (EMEA/CVMP/133/99)

[1] This guideline shall not apply to Marketing Authorisations granted in accordance with Article 13 (1) (a) (i or iii) of Directive 2001/82/EC

2.1 Antimicrobial class

The antimicrobial class should be stated.

2.2 Mode and mechanism of action

The mode and mechanism of action of the antimicrobial substance on the target bacteria should be reported.

2.3 Antimicrobial spectrum of activity

The spectrum of the antimicrobial activity of the substance should be defined. Naturally resistant bacterial species relevant to the use of the veterinary medicinal product should be reported.

2.4 Minimum Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC)

2.4.1 MIC

MIC is the lowest concentration (expressed in µg/ml or mg/l) of antimicrobial substance which, under defined *in vitro* conditions, prevents the growth of bacteria.

MIC values should be determined using accepted standardised methodology. Dilution methods should be used.

The number of isolates for MIC determinations should be scientifically justified and representative of the EU area. In particular, an application for a marketing authorisation for a veterinary medicinal product under the centralised procedure or mutual recognition procedure should consider strains from different European regions. The strains of target animal pathogens to be tested should have been isolated only in the five years prior to the submission of the application. Wherever possible, strains should be epidemiologically unrelated (*e.g.* not coming from the same episode of disease or the same herd) and as representative as possible of a broad geographic area, taking also into account the distribution of husbandry activities. The origin of the isolates used and date of collection should be stated, as well as the way in which they were selected, *i.e.* whether they originated from clinical cases or subclinical carriers. Special attention should be paid to micro-organisms which display a different pattern of susceptibility than would be predicted on theoretical grounds.

The distribution, MIC_{50} and MIC_{90} for all the isolates tested should be reported. Where field isolates show a bimodal or multimodal distribution distinguishing susceptible and resistant isolates, the MIC_{90} should be determined against the susceptible population reporting the percentage of resistance strains separately (see section 4).

2.4.2 MBC

The MBC of the antimicrobial substance for isolates of the target bacteria should be determined if the antimicrobial substance has bactericidal activity. MBC is the lowest concentration of an antimicrobial substance (expressed in µg/ml or mg/l) which, under defined *in vitro* conditions, reduces bacterial counts by 99.9%.

2.5 Kinetics of bacterial killing

Data on the kinetics of bacterial killing should be provided to enable the action of the antimicrobial against the target bacteria to be characterised.

2.5.1 Bactericidal action and bacteriostatic action

- An antimicrobial substance has a bactericidal action against the target bacteria when it kills the bacteria. The MBC is close to the MIC.
- An antimicrobial substance has bacteriostatic action against the target bacteria when the substance inhibits its growth. Here the MBC is currently not determined or is much greater than the MIC

2.5.2 Time-dependency, concentration dependency or co-dependency

Relevant data should be provided for the antimicrobial substance to demonstrate whether its antimicrobial activity is time dependent, concentration dependent or co-dependent for concentration and time. Where available, publications providing information on the pharmacodynamic activity of the antimicrobial, can be used in place of new, supplementary studies.

- Time-dependent antimicrobials

The efficacy of time-dependent antimicrobials is dependent upon the period of time, during which the concentration of the antimicrobial substance exceeds the MIC, but for which concentrations of several magnitudes of the MIC do not increase efficacy.

- Concentration-dependent antimicrobials

The efficacy of concentration-dependent antimicrobials increases when administered at doses which confer concentrations several times the MIC. High concentrations have also been shown to decrease selection of resistance in some classes of antimicrobials.

- Co-dependent antimicrobials

The efficacy of co-dependent antimicrobials depends upon concentrations above the MIC and the period of time during which the concentration of the antimicrobial substance exceeds the MIC. Either factor may dominate in importance but both are important for establishing efficacy

2.6 Post antibiotic effect (PAE)

The PAE is the period of persistent suppression of bacterial growth (after a brief exposure to antimicrobial substance) after the concentration of antimicrobial substance has diminished below the MIC.

For those antimicrobials for which PAE exists, the PAE exerted by the antimicrobial substance against certain bacterial species should be addressed as it may influence the selection of the dose interval of administration. Presence of PAE should be addressed when justifying dosing interval for clinical studies.

2.7 Other information

Some environmental factors (e.g. pH, O_2, inhibitors, cation concentration) may influence the antimicrobial activity in certain infection sites and biological fluids. When available and if relevant to the proposed indications for use of the antimicrobial substance, these data should be reported.

3. PK-PD ANALYSIS

Pharmacokinetic-pharmacodynamic (PK-PD) analysis aims at finding the best correlation between clinical cure and bacterial killing. The PK-PD analysis should be carried out in order to select an appropriate strategy of administration, to optimise dosage, to achieve optimal efficacy and to minimise the development of resistance. When the product is aimed against more than one pathogen which are

part of the same therapeutic indication, it may be useful, within the context of PK-PD analysis, to identify the bacterial species which is dose-limiting.

PK-PD modelling for antimicrobial substances helps to establish the relationships between the dose and the concentration, and between the concentration and the effect on the target bacterial population. Data from PK-PD studies should be used to justify the dosages to be used in the dose-determination studies (predictive approach of PK-PD models). However, the PK-PD relationship is required to be confirmed by dose confirmation studies and clinical field trials.

Currently the most appropriate PK-PD approaches are based on C_{max}/MIC (maximum concentration in serum or plasma/MIC), T > MIC (time during which the concentration exceeds the MIC)and AUC/MIC by convention referred to as AUIC (area under the inhibitory concentration time curve). These variables are derived from animal studies. The MIC used in the calculations is that of the isolate used to infect the animal. Choice of the field isolate should be justified and its MIC should be representative for the susceptible population of bacterial species.

It may be appropriate to use concentrations of the active substance in tissue or other biological fluid than those in serum or in plasma in PK-PD studies. However this should be fully justified with reference to the subcellular site of infection of the target pathogen.

In animal models the comparison of a single administration to a number of administrations while keeping the same overall dosage may differentiate between concentration- and time-dependency of a given antimicrobial substance. When the AUCs are different, other strategies with different C_{max} or T>MIC_{90} may have to be adopted, comparing the administration of a single large bolus to that of the same dose given by infusion or other appropriate form of administration which confer a plasma concentration above, or as some multiple of, the MIC_{90}.

4. RESISTANCE

The likelihood of development of antimicrobial resistance and the mechanisms by which it occurs should be analysed and described as thoroughly as possible. Cross reference can be made to the information supplied in accordance with the *Guideline on pre-authorisation studies to assess the potential for resistance resulting from the use of antimicrobial veterinary medicinal products* (EMEA/CVMP/244/01-FINAL-corr). The applicant should give consideration to the following:

4.1 Resistance mechanisms

- Acquired resistance mechanisms, genetics and resistance transfer in the target pathogens.
- Occurrence of cross resistance and/or co-resistance

4.2 Breakpoints

- MIC distribution of recent representative isolates of target pathogens. The proportion of resistant isolates and breakpoints used should be reported (see section 2.4.1).
- Breakpoints for the specific veterinary pathogens. In case of lack of specific breakpoints for some target pathogens, the applicant should report and justify the methods used to identify the proportion of resistant strains.

5. CLINICAL STUDIES

5.1 General Principles

The principles of GLP, (possible for dose-determination and dose-confirmation studies) or good clinical practice (GCP) should apply to all studies (see VICH Guideline 9 - Good Clinical Practice).

All studies should be controlled studies and the choice of control should be justified.

Clinical trials fall into two categories:

- dose-determination and dose-confirmation studies that determine an optimal dosage and demonstrate efficacy in relation to the claims; these should be conducted under controlled conditions ,
- field trials that, among other things, confirm efficacy results from dose-determination and dose-confirmation studies under practical field conditions.

The type of indication, effective dose, therapeutic scheme and the duration of administration of the antimicrobial product should always be justified. Clinical trials are necessary to demonstrate the therapeutic efficacy for each proposed indication in each target animal species claimed. The number of clinical trials will depend on the type of the antimicrobial and nature of the disease as well as on the reliability of the methods used to assess the outcome. Several controlled trials are generally required.

Appropriate statistical methods should be used (See Note for Guidance on Statistical Principles for Veterinary Clinical Trials (EMEA/CVMP/816/00)).

The product formulation used should be the one proposed for authorisation. Any deviation should be justified. If a formulation other than the one applied for was used in the field trials, bioequivalence has to be demonstrated.

The method of determining the disease and clinical condition of the animals should be appropriate and fully described.

The criteria used to assess the outcome of disease and/or infection should be fully described: clinical, and bacteriological criteria, results from autopsy and other relevant variables can be used. Where appropriate, the description should include steps to confirm the elimination of the target pathogens. As a general rule the design of the clinical study should include appropriate bacteriological sampling before (as part of the inclusion criteria) and after the end of the treatment (as part of the efficacy evaluation). For the treatment claims the treatment should only start after the onset of clinical signs. The time-point for the post-treatment sampling should be justified. Target pathogens isolated in post-treatment samples should be tested for *in vitro* susceptibility. A trend in the selection of resistant isolates or the absence thereof should be discussed.

5.2 Dose-determination studies

Dose determination studies encompass dose level, dosing interval and duration of treatment.

Where possible, experimentally induced infections should be used in the dose-determination studies. The *in vitro* susceptibility of the experimental bacterial strain(s) to the antimicrobial studied should be reported. If no experimental model is available and if study conditions are well controlled, naturally infected animals can be used.

Usually three levels of dosage of the veterinary medicinal product should be tested. Consideration should be given to testing different dosing intervals and durations of treatment. From the results of dose-determination studies and on the basis of predetermined efficacy criteria, the applicant should decide upon a single dosage regimen which should be pursued in confirmation studies and subsequent field trials.

It is recommended to use samples collected during dose-determination studies to generate bacteriological and pharmacokinetic data (prospective approach of PK-PD modelling).

5.3 Dose-confirmation studies

The aim of dose-confirmation studies is to confirm the efficacy of the selected dosage regimen in animals or groups of animals under controlled clinical conditions. These studies can be performed using experimental models of infections but well controlled studies using naturally infected animals are preferred.

Efficacy criteria used to assess the outcome of disease and/or infection are similar to those for dose-determination studies. When progressing from dose-determination to dose-confirmation studies, it is possible to add further efficacy criteria, but not to exclude any.

5.4 Field trials

Field trials should be multicentric and conducted in naturally infected animals. For a given indication, the study population should be representative of the target population and the sample size should be justified.

If a product exists, authorised under Council Directive 2001/82 for the same indication then this should be used as reference. If an untreated (placebo) group is included, the welfare of animals in the study must be given the highest priority.

Clinical trials should incorporate strictly defined clinical and microbiological criteria for both inclusion and success criteria. When technically feasible, isolation of the target pathogen from the animals or a representative proportion of them is required at the time of inclusion. Sampling should be performed before starting treatment, and positive isolation leads to the confirmation of inclusion. Susceptibility of the isolated bacteria to the test product (and to the reference product, where appropriate) should be tested *in vitro.*

Information on concomitant viral or parasitic infections should be provided, where appropriate.

Response to therapy must be based on clinical and microbiological criteria wherever possible. The time points and methods to assess the effects of treatment in field cases should be explained and justified.

The choice of the clinical endpoint is critical and determines the study design. Post-treatment follow-up should be performed for a sufficient time after the effects of treatment would be expected to have ceased. This should be done in order to allow for any relapse to occur and to assess the final outcome. Clinical failures should be addressed in detail.

5.5 Other points to consider

The principles as outlined in chapter 5 General Principles regarding the demonstration of clinical efficacy also apply to group medication and combination therapies.

For a claim at group level, the extent to which the infection is present before administration of treatment should be defined in the protocol and justified. Where applicable, in the course of the study the disease (clinical signs and positive bacteriological findings of the target pathogen in a justified proportion of the animals) should appear and spread in a significant proportion of the non-treated or placebo group in order to draw a conclusion on the efficacy of the product.

For fixed combinations please see *Note for Guidance on Fixed Combination Products* (Volume 7A, guideline III/3730/90).

6. SPC

The SPC should be drafted taking into account the guidance in the Notice to Applicants (Volume 6B) and *Guideline on the SPC for veterinary medicinal products containing antimicrobial substances* (EMEA/CVMP/612/01).

It is emphasised that if a disease and/or infection is the result of associated activity of several pathogens attention should be paid on the wording of the indication. It should be made clear that the veterinary medicinal product is only intended to be used in diseases caused by micro-organisms, which are proven or strongly suspected to be susceptible to the active substance. The clinical indications for use of a new product have to be formulated accordingly.