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# Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

## Revision

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This guideline replaces the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/2001)

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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# Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

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# Executive summary

This guideline provides recommendations for the design and conduct of pre-clinical and clinical studies to support clinical efficacy for an antimicrobial[1] veterinary medicinal product. Appropriate methods to identify and describe the pharmacology of the active substance in relation to the target bacteria are presented and important aspects to consider for justifying the use of a certain active substance for a particular indication are outlined. Advice regarding study design, selection of comparator and efficacy endpoints is given for the purpose of gaining conclusive study results for the intended claim which could be treatment, treatment and metaphylaxis, or prevention.

# 1. Introduction (background)

The objective of this guideline is to specify the data required to demonstrate the therapeutic efficacy of a veterinary medicinal product (VMP) containing an antimicrobial agent for (a) given indication(s) using an appropriate therapeutic regimen. Thus, the following sections provide guidance on the essential topics which the applicant should cover in order to demonstrate efficacy i.e. pharmacodynamics (including resistance mechanisms), pharmacokinetics and clinical trials. In the context of this guideline an antimicrobial is defined as a substance primarily acting against bacteria.

# 2. Scope

This guideline applies to antimicrobial substances used in veterinary medicines for all routes of administration and to all pharmaceutical forms. For antimicrobials intended for intramammary administration the Guideline for the Conduct of Efficacy Studies for Intramammary Products for Use in Cattle (EMEA/CVMP/344/99) should also be considered. For fixed combinations please see also the CVMP Guideline on pharmaceutical Fixed Combination Products (EMEA/CVMP/83804/2005).

This guideline applies to all new applications for marketing authorisations for veterinary medicinal products containing new antimicrobial substances or antimicrobial substances contained in veterinary products already authorised such as variations or extensions to include new indications or a new target species. The guideline does not address applications for generic products when according to current legislation efficacy studies for those applications are not required.

The guideline does not apply to products containing an antimicrobial agent if the indication is not for combating a bacterial infection. However, for such products safety issues like development of resistance needs to be addressed as outlined in this and other relevant guidelines.

# 3. Legal basis

This Guideline replaces the current CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/2001), and should be read in conjunction with Directive 2001/82/EC, as amended. Applicants should also refer to other relevant European and VICH guidelines, including those listed in the reference list of this document.

[1] Antimicrobial agent: A naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable *in vivo*. Antiparasitics and substances classed as disinfectants or antiseptics are excluded from this definition (OIE Terrestrial Animal Health Code definition). In the context of this guideline the focus is on compounds acting against bacteria.

# 4. General considerations

Antimicrobials are powerful tools, fundamental to combat bacterial infections in animals. However, all use will inevitably select for antimicrobial resistance. Thus it is vital that all unnecessary or inadequate use is avoided, in order to prolong the time period during which the compound in the proposed dose will remain effective. In addition, potential risks to public health need to be considered.

The following is to be specifically addressed in order to justify the need/s and selection of an antimicrobial in relation to the indication investigated in the clinical development program:

- The indication should be justified. Use of antimicrobials for treatment of mild and transient infections that will resolve independent of treatment will be questioned. In case of multi-factorial diseases, efforts should be made to describe the expected contribution from the antimicrobial treatment and studies should be designed considering where and when there is a place for an antimicrobial in the treatment strategy.
- The target population for therapy should be well defined and possible to identify under field conditions. The study population in field trials should reflect the intended target population for therapy.
- Official guidance on preferred choices of antimicrobials to be used and those to be reserved for certain conditions such as CVMP recommendations[2] (when available) should be considered when taking decisions on which populations to include in the studies. For example, fluoroquinolones and third and fourth generation cephalosporins are recommended to be used only in cases that have responded poorly or are expected to respond poorly to other antimicrobials and this limits the target population for these classes.
- The dose, the dosing interval and the number of administrations of the antimicrobial product should always be justified by considering the pharmacodynamic/pharmacokinetic (PK/PD) relationship, if established, as well as the severity of the disease. To avoid unnecessary exposure to antimicrobials (and thus unnecessary selection pressure for resistant bacteria), the duration of exposure should not be longer than necessary to accomplish the desired outcome.

# 5. Pharmacology

The pharmacokinetic and pharmacodynamic properties of the active moiety should be adequately documented.

For the conduct of pharmacokinetic studies please see the CVMP Guideline on conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99). Studies on pharmacodynamics should be performed according to validated and internationally accepted methods, and according to Good Laboratory Practice (GLP), when applicable. Data requirements are detailed below.

## *5.1. Antimicrobial class*

The antimicrobial class should be stated.

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000384.jsp&mid=WC0b01ac058002dd37#Antimicrobials

## 5.2. Mode and mechanism of action

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

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

## 5.3. Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) is the lowest concentration (expressed in µg/ml or mg/l) of an antimicrobial substance which, under defined *in vitro* conditions, prevents the visible growth of bacteria. MIC values should be determined using accepted standardised methodology. Dilution methods, when available, should be used and the methods clearly described. However, it is recognised that to date standardised methodologies are not available for all organisms.

MIC data should be provided for all target bacteria. A representative number of clinical isolates of each target bacteria should be collected, to allow detection of isolates with MICs deviating from the normal distribution of strains without any acquired resistance (wild type). For rare pathogens a lower number of isolates could be justified than for commonly encountered pathogens. The isolates of the target bacteria to be tested should have been collected within five years prior to the submission of the application. Isolates should be epidemiologically unrelated (not coming from the same episode of disease in the same herd or same animals) and constitute a representative sample from within the EU. For bacteria isolated from food-producing animals, selection of livestock farms should include units of different type, size and production intensity. The tested isolates should come from the animal subgroup(s) or production type(s) that are targeted in view of the indication (e.g., weaning piglets, veal calves etc.). The origin of the isolates investigated (animal species, condition, farm type, geographic area) and dates of collection should be stated.

The susceptibility for antimicrobials varies not only between different bacterial species but also between strains and over time. The complete MIC distribution data for all isolates tested of each bacterial species should be reported in tables and if relevant, divided by subgroups (country, region, husbandry type, etc.). In case the MIC distribution indicates the presence of subtypes of bacteria with reduced susceptibility (bi or multimodal distribution), these should be further discussed and compared with already available (historical) data to allow conclusions to be drawn on acquired resistance. The subpopulation of less susceptible bacteria needs to be further characterized to allow for conclusions on whether it will be included in the intended population to be treated, or not. It is acknowledged that for historical data information of the full distribution may not be available. In such cases all available data such as $MIC_{50}$ and $MIC_{90}$ should be provided.

The data on MIC distribution should be interpreted using adequate interpretation criteria. The epidemiological cut-off value should be determined, if feasible, to define the population without any acquired resistance. The epidemiological cut-off value can be proposed as the clinical breakpoint. In case a population with reduced susceptibility is identified the applicant can suggest a clinical breakpoint (i.e. a MIC value under which the selected dose is shown efficient) deviating from the epidemiological cut-off value. Any such clinical breakpoint must be supported by microbiological, clinical and available PK/PD data and the dose should be selected accordingly (see dose finding below). In case reference is made to a clinical breakpoint established by an external institute or published in literature it should be demonstrated that this value is relevant for the product under study.

It is recommended to include also major metabolites contributing significantly to the antimicrobial activity in the *in vitro* susceptibility testing.

## 5.4. Minimum Bacterial Concentration (MBC) and kinetics of bacterial killing

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%.

Data on the kinetics of bacterial killing should be provided to characterize the action of the antimicrobial against the target bacteria and to demonstrate whether its antimicrobial activity is bacteriostatic or bactericidal and whether it is time-dependent (i.e. 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 (i.e. efficacy increases when administered at doses which confer concentrations several times the MIC) or co-dependent (i.e. which depends both upon concentrations above the MIC and the period of time during which the concentration of the antimicrobial substance exceeds the MIC). This can be bacterium or condition specific and data should be provided for different target pathogens when appropriate. Where available, publications providing information on the pharmacodynamic activity of the antimicrobial can be used as supportive information. Kinetics of bacterial killing should be performed according to validated and internationally accepted methods. The clinical relevance of claimed bactericidal activity against certain target bacteria should be discussed.

## 5.5. Resistance

Isolates with MICs deviating from the normal distribution for a certain antimicrobial class should be tested for cross-resistance. Mechanisms of acquired resistance should be discussed.

Cross-reference can be made to the information supplied in accordance with the VICH GL 27: Guidance on the pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance.

## 5.6. Additional in-vitro studies

Additional *in vitro* studies may include an investigation of possible synergy or antagonism, post-antibiotic effects and, for certain antibacterial agents, an estimate of the rate of selection of resistant mutants and how concentrations above the MIC may affect or prevent mutations. The methods for additional studies should be well described and the clinical relevance of the obtained results should be justified.

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

## 5.7. The pharmacokinetic/pharmacodynamic (PK/PD) relationship

To be effective, the dose of an antimicrobial agent must be selected considering the susceptibility of the target bacteria. Therefore, for all compounds with systemic activity, the MIC data collected should be compared with the concentration of the compound at the relevant biophase following administration at the assumed therapeutic dose as recorded in the pharmacokinetic studies.

Based on *in vitro* susceptibility data, and target animal PK data, an analysis for the PK/PD relationship may be used to support dose regimen selection and interpretation criteria for resistance. In circumstances in which it is not feasible to generate extensive clinical efficacy data (e.g. in rare types

of infections or against rare types of pathogens, including multidrug resistant pathogens that are rarely encountered) PK/PD analyses may also provide important supportive information on the likely efficacy of the test antibacterial agent.

The overall assessment of the PK/PD relationship should be sufficiently comprehensive to assess with reasonable confidence whether or not the test antibacterial agent, when used at an adequate dose regimen, would show clinical efficacy against claimed target pathogens that appear to be susceptible *in vitro*.

It is acknowledged that the PK/PD analyses will be based on PK data obtained from healthy or experimentally infected animals. Nevertheless, the sponsor is encouraged to collect PK data from naturally diseased animals using population kinetic models. Knowledge of kinetic variability considerably increases the value of the PK/PD-analysis.

In some cases where the PK/PD relationship is well established using validated models, it may be possible to omit dose-determination studies and to evaluate in a clinical trial the efficacy of one or a very few regimens. However, to be acceptable the choice of the PK/PD parameter considered as best predictive of efficacy must be prospectively justified by independent data. In addition, the use of PK/PD to predict the optimal duration of treatment is not well established at present and sponsors should consider whether preliminary regimen-finding studies are needed to identify a suitable duration of treatment for any one indication.

Currently the most commonly used parameters to express the PK/PD relationship are $C_{max}$/MIC (maximum concentration in serum or plasma/MIC), %T > MIC (fraction of time during which the concentration exceeds the MIC) and AUC/MIC by convention referred to as AUIC (area under the inhibitory concentration time curve). Use of free (unbound) fraction is normally required for calculation of PK/PD parameters.

PK data from other matrices than plasma might be used provided there are validated models available.

# 6. Clinical studies

## *6.1. General Principles*

It is recommended to conduct preclinical and clinical studies according to Good Laboratory Practice (GLP) and/ or Good Clinical Practice (GCP). In case GLP and/or GCP is not applied, traceability and integrity of data should be adequately guaranteed by other means. For clinical field trials, GCP status is required.

All studies should be controlled studies and the choice of control should be justified. When conducting pre-clinical studies, the “3R-principles” (replacement, reduction, refinement) should be considered.

Clinical trials should cover each proposed indication and bacterial species in each target animal species claimed. The number of clinical trials will depend on the type of veterinary medicinal product and nature of the disease. Several controlled trials are generally required dependent on the size and quality of studies conducted.

Appropriate statistical methods should be used (see CVMP Guideline on statistical principles for veterinary clinical trials, CVMP/EWP/81976/2010).

The product formulation used should be the one proposed for authorisation. Any deviation should be justified. If the formulation used in the field trials differs from the final formulation, the relative bioavailability should be documented.

The method of determining the disease and clinical condition of the animals should be appropriate and fully described. Whenever possible, established methods for diagnosis should be applied.

Principally there are three different kinds of claims:

- For **treatment** claims the VMP should only be administered after the onset of clinical signs and only clinically affected individuals are to be treated.
- **Metaphylactic** claims are when in addition to treatment of clinically affected animals there is a need for administration of an antimicrobial to other animals in the same group, still clinically healthy but likely to be infected due to close contact with diseased animals.
- **Preventive** claims refer to administration of a VMP to healthy animals to prevent infection.

## *6.2. Dose-determination studies*

Detailed information about an adequate therapeutic scheme for each bacterial species and claim should be collected from experimental studies performed under controlled conditions. Dose determination studies encompass dose level, dosing interval and number of administrations. They are important to ensure efficacy of the product without unnecessary exposure to the compound.

Dose determination studies should always include a negative control. Appropriate measures should be applied to ensure animals welfare.

Where possible, experimentally induced infections should be used in the dose-determination studies. The origin and *in vitro* susceptibility of the strains used in the study should be presented (see section 5.4). The susceptibility should be representative of the bacterial population against which treatment is aimed to be effective. In case a claim is made against bacteria with reduced susceptibility relative to the wild type distribution this should be taken into account when selecting the test strain. In case several primary pathogens will be included in the sought indication (e.g. bovine respiratory disease); dose determination should be based on the least susceptible species as evident from relevant data. In case this is not possible due to lack of established experimental model conclusive information regarding the treatment effect for the least susceptible species needs to be presented from dose confirmation and/or clinical studies. The validity of the experimental models used should be justified with regard to their capability to establish infection and cause clinical disease similar to naturally infected animals. In case of therapeutic treatment claims, the drug administration should not be initiated before the clinical signs relating to bacterial infection are observed.

If no experimental model is available and study conditions are well controlled, naturally infected animals can be used.

It is recommended to include PK data in dose finding studies to allow the recorded effects to be related not only to dose but more specifically to time-concentration curves during treatments.

Usually three levels of dosage of the veterinary medicinal product should be tested, preferably using the final formulation.

Consideration should be given to testing different dosing intervals and different number of administrations. If it is not feasible to perform studies to explore different dosing strategies, the recommended dosing interval and treatment duration could be justified on basis of the time course of disease progress. In addition, the PK and PD characteristics of the active substance should be considered, including considerations of the balance between sufficient efficacy for the target bacteria species and the risk for resistance development. When available, data from published clinical studies

comparing different regimens for a similar product/drug class may be used to support the need for a certain duration of exposure.

Efficacy endpoints should include the clinical and bacteriological response as determined by use of appropriate clinical, post mortem and bacteriological diagnostic methods, and the determination of mortality rate. The endpoints (primary and secondary) used should be justified in relation to the disease and substance under study. Observations should be collected repeatedly before, during and after treatment. The time of response assessment should be selected so as to distinguish between the effect of the treatment and the natural course of the disease.

Statistical comparisons between different dose levels groups and the negative control group should be provided if possible, although it is acknowledged that dose determination studies are often not dimensioned to generate statistical support and thus conclusions are often based on descriptive information.

From the results of dose-determination studies, the applicant could decide upon an appropriate dosage regimen which should be pursued in confirmation studies and subsequent field trials.

**Locally acting products**

The dosing regimen should be substantiated also for locally active products. In the case of formulations applied directly to the infection site and which do not undergo significant dilution, a justification can be sufficient, taking into account the product strength, the formulation and *in vitro* susceptibility data for the target bacteria. In other cases, such as e.g. locally active products for the gastro-intestinal tract clinical dose finding studies should be performed as detailed above. Notably, the extent of systemic absorptions is one aspect limiting the upper dose for a locally active compound. For details on intramammary products, please see the CVMP Guideline for the conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/344/99-FINAL-Rev.1) Regarding systemically administered products intended to combat a localized infection (e.g. metritis) the dose should be established according to recommendations given in the previous section.

## *6.3. Dose-confirmation studies*

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

The study should preferably include a negative control group. Sufficient rescue protocols need to be implemented to take account of any animal welfare concerns. For treatment claims, in case the use of a negative control is not possible an appropriate positive control may be acceptable provided internal validity and sensitivity of the study is ensured.

Efficacy criteria used to assess the outcome of disease and/or infection are similar to those for dose-determination studies. The primary endpoint(s) should preferably be the same as those intended for use in the field trials.

Dose confirmation studies may allow for the assessment of relapse rate. Relapse rate, assessed by clinical and/or bacteriological endpoints as appropriate should be determined at a time point outside the period of pharmacologically active levels in the target tissue and where the condition of the animal could still be related to the effect of treatment whereas the risk for re-infection to have occurred is low. The time selected should be justified in this respect.

It can be acceptable to waive dose-confirmation studies provided all of the following criteria are fulfilled:

- the conditions of the dose determination studies are representative of the field conditions in terms of the type of infection and the animals involved,
- the susceptibility pattern for any challenge strain used for dose determination is relevant for the field situation,
- a clear dose-effect relationship is documented as supported by adequate dose determination data,
- the dose determination data allows for the selection of one appropriate dose level,
- the dosing interval and the number of administrations is adequately justified.

At least one dose confirmation study must be presented in case dose finding is based on *in vitro* PD data only.

For group/flock medication composition, intake and also variability in feed/water intake should be considered when confirming the dose. Alternatively, population PK/PD models (such as Monte Carlo simulations) based on data from field trials could be used for this purpose.

## *6.4. Field trials*

### 6.4.1. Study design and population

Field trials should be multicentric, randomized, blinded and controlled, and conducted in naturally infected animals. For a given indication, the study population should be well defined, and representative of the intended target population for therapy. This includes considerations regarding housing conditions, production forms and geographical location. Furthermore the sample size should be justified See point 4 general considerations, above and the CVMP Guideline on statistical principles for veterinary clinical trials (reference list).

### 6.4.2. Control

**Negative control**

Including a placebo or an untreated control group may be of value in conditions with high self-cure rate since the risk for erroneous conclusions is high in these situations. Negatively controlled studies can be useful when there are no approved products for the indication in question to serve as control, or in the case of treatment of infections with bacteria resistant to previously authorized substances. A negatively controlled study is always necessary to support a prevention claim and in some situations also to gain support for a metaphylactic claim (see separate sections). Blinding of the study needs to be ensured through appropriate study design measures such as placebo treatment.

The welfare of animals in the study must be given the highest priority, e.g. through the establishment of appropriate exit clauses and rescue protocols.

**Positive control**

A positive control should be a product authorised under Council Directive 2001/82/EU, as amended, for the same indication. The applicant should justify that the chosen control can be considered as an effective treatment for the target indication. Use of the chosen control product should be justified based on information about the susceptibility of the target pathogens for the compound.

Susceptibility of the target pathogens might differ between regions and over time. Products for which recent susceptibility data suggest that posology may be inadequate for the infection under study, or products where posology differs between member states should be avoided. A comparator should always be used according to the label instructions.

Since it is of vital importance that the positive control is appropriate it is recommended that advice is sought from the authorities if the relevance of the tentative control product is uncertain.

When a study is performed to explore non-inferiority of the test product, appropriateness of the study design should be ensured and the non-inferiority limit should be pre-specified and justified from a clinical relevance perspective, according to the statistical principles outlined in the relevant CVMP Guideline (CVMP/EWP/81976/2010). It should further be ensured that the current study design is appropriate in the sense that it can be reliably expected that a recognized level of efficacy will be demonstrated for the control treatment.

In case the aim is to demonstrate superiority as compared to a previously authorized product it has to be ensured that the positive control is a relevant treatment alternative for the current indication at the time of investigation (see above). This would include the presentation of susceptibility data for the control to ensure that any difference is not dependent on resistance development.

A superiority trial with regard to an existing control product is a valuable means to support efficacy where the target population corresponds to clinical conditions of particular severity and where there is reasons to suspect that approved products would not be sufficiently effective.

### 6.4.3. Inclusion criteria

Clinical trials should incorporate strictly defined clinical and microbiological inclusion criteria as appropriate for the claimed indication. Susceptibility of the isolated bacteria to the test product (and to the control product, where applicable) should be tested *in vitro*.

When the aim is to confirm efficacy against one or several specified bacteria, isolation of the target pathogen(s) from the animals or a representative proportion of them is required at the time of inclusion.

In case individual bacteriological testing of all included animals is not feasible (e.g. herd treatment), the sample size should be large enough to allow confirmation of the etiological diagnosis with sufficient level of certainty. For those animals which are included on basis of clinical signs only, the causal relationship to the target bacterium should be made evident through appropriate clinical diagnostic criteria.

The microbiological sampling technique used on all or a proportion of the study animals should be justified and valid in the sense that it accurately reflects the infectious status of the animal (see also section 6.4.4).

The inclusion criteria should be selected to ensure that the study population reflects the intended target population in the best possible way. Any deviation should be justified in consideration of possible differences in clinical outcome between the two populations.

In diseases characterized by presence of more than one bacterial species (e.g. metritis), inclusion may be based mainly on clinical signs. However, to support the clinical diagnosis samples should be collected from the animals or a relevant portion of the included animals to clarify which bacteria are involved in the disease process, and the susceptibility pattern should be tested *in vitro* for the most commonly occurring pathogens.

### 6.4.4. Exclusion criteria

Animals where the effect assessment could be biased from any previous or concomitant treatment should be excluded from the trial. Appropriate and justified time intervals between previous treatment and study inclusion should be applied. Any other relevant exclusion criteria, dependent on infection to be treated, can be established. These criteria will help defining the target population in any future marketing authorisation.

### 6.4.5. Concomitant diseases

Information on concomitant viral, fungal or parasitic infections should be provided, where appropriate so that the impact on the study results of these potential confounding factors can be evaluated.

### 6.4.6. Endpoints and timing of efficacy assessment

Response to therapy should be based on clinical response criteria and microbiological criteria as appropriate for the specific disease under study. 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. The primary variable, also known as the primary endpoint variable, should be the variable capable of providing the clinically most relevant and convincing evidence directly related to the primary objective of the trial and a justification in this respect will be expected.

Clinical cure rate following appropriate diagnostic procedures is in most situations the preferred primary endpoint. However, depending on the epidemiology and pathogenicity of the disease, microbiological cure rate may also be highly relevant and sometimes necessary as a primary or co-primary endpoint. Support from relevant secondary endpoints will often be necessary to justify a claim.

When efficacy assessment on an individual level is not applicable, such as in claims for chicken, treatment success is to be evaluated on group/herd level through relevant efficacy endpoints such as a change in mortality rate. Post mortem examinations including bacteriological sampling are necessary to explore treatment effect in these situations.

To assess the final outcome, post-treatment follow-up should be performed for a sufficient time after the effects of treatment would be expected to have ceased i.e. when sub-therapeutic concentrations have been reached in plasma or target tissue. Clinical failures identified at time of primary effect assessment and at time of post-treatment follow-up should be addressed in detail. The timing of follow-up measurement should be appropriate to allow the detection of relapses (reoccurrence of clinical disease in initially clinically cured animals) related to insufficient effect of treatment but avoiding the inclusion of re-infected animals. A decision on appropriate timing should be based on data regarding treatment effect duration and information on the dynamics of the disease. Bacterial sampling and susceptibility tests from clinical failures and relapses should be performed, if feasible.

### 6.4.7. Special considerations for metaphylaxis claims

In outbreaks of infections in a herd/unit where the causative agent is known to spread quickly and cause clinical disease in a large proportion of the stock within a short time span, simultaneous treatment of clinically diseased animals and metaphylactic treatment of clinically healthy animals likely to be in the incubation phase due to close contact with diseased animals may be justified from an epidemiological point of view The objective would be to control disease spread and prevent further development of clinical signs in the group.

A metaphylaxis claim is only accepted in conjunction with a treatment claim and never as a separate indication. Some formulations (e.g. oral powders for drinking water) allow only a combination of treatment and metaphylactic claims as all animals will be treated independent of individual clinical status, whereas other formulations like injectables may be approved either for treatment or for treatment and metaphylaxis.

In case the study formulation is to be used for group/flock administration only (such as oral powders for drinking water), standard principles for study design will be applicable (see above) using relevant efficacy endpoints to document treatment success. In cases where treatment and metaphylaxis cannot be distinguished due to the fact that individual monitoring of the health condition is not possible as may be the case for group treatment of e.g. chicken and fish, , a metaphylaxis claim will be accepted in addition to a treatment claim if convincing efficacy data on group level are presented.

A metaphylactic claim can also be approved for animals in a group that are treated individually. The potential need for metaphylaxis will depend on the epidemiology of the disease under study. Efficacy of metaphylaxis does not need to be separately tested in a clinical trial in cases where it is made evident that treatment would effectively stop any further development of clinical cases. Bibliographic data documenting the disease characteristics and epidemiology may be used to support a metaphylaxis claim. In such cases the treatment effect would only have to be documented in clinically affected individuals and it could be assumed that the metaphylactic efficacy, defined by the same tentative endpoints, would not be less than efficacy of treatment of clinically affected animals.

In cases where for a product intended for individual treatment insufficient information is available to support a metaphylaxis claim, clinical data should be provided. When designing such clinical studies the following should be specifically considered:

- The need for metaphylaxis should be discussed and the threshold for the initiation of metaphylactic treatment (e.g. the proportion of clinically diseased animals at a certain time point within a group) should be justified on epidemiological grounds and reflected in the clinical trial protocol.
- The primary endpoint should be the clinical health status of the animals as measured by appropriate parameters.
- The estimated magnitude of effect should be justified from a clinical perspective.
- Non antimicrobial supportive treatment should be allowed in the treatment and the placebo group.
- The follow-up period should be sufficient to conclude on the efficacy for prevention of clinical disease in unaffected but treated animals.
- Well managed herds should be included to ensure that any observed positive effect of metaphylactic treatment is not related to poor management conditions.
- Studies should be negatively controlled.
- The effect of metaphylaxis and treatment may be documented in the same study. If so, efficacy must be recorded on individual level and treatment outcome should be presented separately for the two groups (diseased animals and animals with no clinical signs but at risk of developing clinical disease. In case the treatment effect is evaluated through comparison with an authorized product, a negative group needs to be included to evaluate efficacy regarding the metaphylaxis claim.

### 6.4.8. Special considerations for preventive claims

Preventive claims refer to the administration of a VMP to healthy animals to prevent infection. Such claims should only be considered in those situations when the risk for infection is very high and the consequences are severe. The need for prevention must be fully justified for each target species and indication.

To support a preventive claim a negatively controlled study is always needed and animal welfare should be accounted for through the acceptance of adequate supportive treatment in both test and control group and implementation of rescue protocols. The criteria used to assess the outcome of disease and/or infection should be fully described.

The timing of treatment in relation to the expected time of exposure to infectious agents should be justified in consideration of the duration of the therapeutic effect of the product under study.

Study animals should be kept in well managed conditions to ensure that bias is not introduced through poor environment.

## 7. Summary of product characteristics (SPC)

The SPC should be drafted taking into account the guidance in the Notice to Applicants (Volume 6C) and the revised CVMP Guideline on the SPC for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/SAGAM/383441/2005). Recommendations presented by CVMP for different classes of antimicrobials should be considered.

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 intended to be used only in diseases caused by micro-organisms, which are proven or strongly suspected to be susceptible to the active substance.

## References


Directive 2001/82/EC

CVMP Guideline for the conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/344/99)

CVMP Note for Guidance on fixed combination products (EMEA/CVMP/83804/05)

CVMP Guideline on statistical principles for veterinary clinical trials (CVMP/EWP/81976/2010)

CVMP Guideline on the SPC for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/SAGAM/383441/2005)

CVMP strategy on antimicrobials 2011-2015 (EMA/CVMP/287420/2010)

VICH Guideline 27 (GL 27): Guidance on the pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance

VICH Guideline 9 (GL 9): Good Clinical Practice (CVMP/VICH/595/1998)

Good Laboratory Practice (GLP) (see Council Directive 88/320/EEC as amended)