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

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This guideline updates the CVMP guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001)

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1. Executive summary

This guideline provides recommendations for the design and conduct of pre-clinical and clinical studies to support clinical efficacy for an antimicrobial[2] veterinary medicinal product (VMP). 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. Alternative study designs may be applied if justified.

2. Introduction (background)

The objective of this guideline is to specify the data required to demonstrate the therapeutic efficacy of a veterinary medicinal product 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. pharmacokinetics (PK), pharmacodynamics (PD) including resistance mechanisms, dose determination and clinical field trials.

In the context of this guideline, an antimicrobial is defined as a substance primarily acting against bacteria.

3. Scope

This guideline applies to antimicrobial substances included in veterinary medicines for all routes of administration and in all pharmaceutical forms. For antimicrobials intended for intramammary administration the pharmacology section (except the PK/PD section, 5.7) of this guideline applies whereas regarding clinical issues only the CVMP guideline for the conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/344/99) would have to be considered. Cross-reference is also made to the CVMP guideline on the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99).

For fixed combinations please see also the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

This guideline applies to all applications where according to Directive 2001/82/EC, new data has to be generated to support clinical efficacy.

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.

4. 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. Directive 2010/63/EC regarding the protection of animals used

[2] 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.

for scientific purposes also applies. Applicants should also refer to other relevant European and VICH guidelines, including those listed in the reference list of this document.

5. General considerations

Antimicrobials are powerful and important tools 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 will remain effective. In addition, potential risks to public health need to be considered such as outlined in separate guidelines (VICH GL27, EMA/CVMP/AWP/706442/2013 – in draft).

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, e.g. through appropriate reference to published information, 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 to the best possible extent.
- Official guidance on preferred choices of antimicrobials to be used and those to be reserved for certain conditions such as CVMP recommendations[3] (when available) should be considered, with an intention to obtain the best achievable alignment between the study population and the target population for treatment. Any deviation from official guidance recommendations should be justified.
- The dose and the dosing interval of the antimicrobial product can be justified by considering the pharmacodynamic/pharmacokinetic (PK/PD) relationship, if established, as well as the severity of the disease, whereas the number of administrations should be in line with the nature 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.

In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied.

6. Pharmacology

The pharmacokinetic and pharmacodynamic properties of the active substance 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). Sufficient pharmacokinetic data should be provided to support the dose regimen and route of administration for the intended

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

authorisation. Where applicable, pharmacokinetic data for the relevant biophase (target site of effect of the substance) should also be supplied for the purposes of determining the PK/PD relationship (see section 6.7). 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.

6.1. Antimicrobial class

The antimicrobial class should be stated.

6.2. 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. Intrinsically resistant bacterial species which may also be associated with disease relevant to the intended use of the veterinary medicinal product should be reported.

If information is available, reference should also be made to actions of the substance which are additional to its microbial killing properties and might contribute to its clinical efficacy, e.g. effects on organism pathogenicity or virulence, anti-inflammatory, immunomodulatory or other effects.

6.3. 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, preferably such as described by EUCAST[4] and, if not available, as in CLSI[5] documents. 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 scientifically justified number of clinical isolates of each target bacteria, representative of the EU area, should be collected to allow detection of isolates with MICs deviating from the normal distribution of isolates 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). For bacteria isolated from food-producing animals, selection of livestock farms should include, where applicable, units of different production types. In these cases, the tested isolates should preferably come from the animal subgroup(s) or production type(s) that reflect the target population for the indication. The origin of the isolates investigated (animal species, clinical condition, production type, geographic area) and dates of collection should be stated.

The susceptibility to antimicrobial substances 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 origin as indicated above. In case the MIC distribution indicates the presence of subtypes of bacteria with reduced susceptibility (bi or multimodal distribution), these should be compared with already available (historical) data to allow

[4] EUCAST - European Committee on Antimicrobial Susceptibility Testing
[5] CLSI - Clinical and Laboratory Standards Institute

conclusions to be drawn on mechanisms for acquired resistance. Based on these conclusions and supportive clinical data, the subpopulation with reduced susceptibility may be included in the intended population to be treated. It is acknowledged that for historical data information on the full MIC distribution may not be available or studies may not have been performed according to the same methodology or interpreted using current interpretative criteria. 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[6] should be provided, if feasible, to define the population without any acquired resistance. Ideally a clinical breakpoint should be proposed by the Applicant. This could be either the epidemiological cut-off value or a clinical breakpoint deviating from the epidemiological cut-off value (i.e. a MIC value under which the selected dose regimen is shown to be effective). Any clinical breakpoint should be supported by microbiological, clinical and available PK/PD data. In case reference is made to a clinical breakpoint established by an external institute or published in literature from peer-reviewed journals, acceptance will depend on the availability of an adequate level of detail to determine if the breakpoint was appropriately characterised. It should also be demonstrated that this value is relevant for the active substance in the formulation under study.

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

6.4. Minimum Bactericidal Concentration (MBC) and kinetics of bacterial killing

Minimum Bactericidal Concentration (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 substance 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). Kinetics of bacterial killing should be performed according to validated and internationally accepted methods using static or dynamic concentration time-kill studies. Preferably all raw data should be provided, ideally including the target biophase. Data can be bacterium or condition specific and should be provided for different target pathogens when appropriate. Where available, publications providing information on the pharmacodynamic activity of the antimicrobial substance can be used as supportive information. The clinical relevance of claimed bactericidal activity against certain target bacteria should be discussed.

6.5. Resistance

Isolates with MICs deviating from the normal distribution for a certain antimicrobial class should be tested for co-resistance and cross-resistance.

[6] For definitions of epidemiological cut-off values and clinical breakpoints, please refer to EUCAST. http://www.srga.org/Eucastwt/eucastdefinitions.htm

Where possible, information on the resistance mechanism(s), the molecular genetic basis of resistance and on the rate of transfer of resistance determinants should be provided and discussed. This information may come from literature from peer-reviewed journals or proprietary studies and may derive from related antimicrobial substances in the absence of data on the specific substance.

Cross-reference can be made to the information supplied in accordance with the guidelines mentioned in section 5.

6.6. Additional in vitro susceptibility studies

Additional *in vitro* susceptibility studies should, whenever relevant, include an investigation of possible synergy or antagonism and may include, for example, investigation of 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 selection of mutants. The methods for additional susceptibility 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 in 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.

Notwithstanding the guidance on the conduct of MIC, MBC and time-kill studies presented in sections 6.3 and 6.4 of this guideline, namely to use internationally recommended guidelines and methodology in *in vitro* studies, any differences between artificial growth matrices (as required for use in international guidelines) and biological fluids, such as serum or heat-treated serum, should be reported for at least a limited number of isolates.

6.7. The pharmacokinetic/pharmacodynamic (PK/PD) relationship

The objective of antimicrobial therapy is to provide an effective drug, in sufficient concentration and maintained for sufficient time at the biophase, to inhibit or kill bacterial target organisms and achieve clinical cure of infection in all affected animals. A justification must be provided for the proposed therapeutic dose of an antimicrobial drug indicating that it will be effective. Thus, for all active antimicrobial substances with systemic activity, establishment of a pharmacokinetic/pharmacodynamic (PK/PD) relationship based on PK and PD data may be used to support selection and optimization of the dose and dosing interval. Knowledge of the PK/PD relationship may also have an important role in preventing the emergence of bacterial resistance and can, therefore, be used to support selection of a clinical breakpoint.

To establish doses for evaluation in clinical trials, use of PK/PD integration approaches (integrating of a PD parameter with one or more PK parameters generated in a separate PK study to predict an effective dose) and/or PK/PD modelling approaches (*in silico* modelling of PD and PK data generated in the same study to select optimal dosage schedules) can be made. Currently the most common integration approaches use PK/PD indices such as 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 curve), to express a PK/PD relationship. If use is made of PK/PD indices, the choice of the PK/PD index considered as best predictive of efficacy should be justified. Further characterisation of PK/PD indices needs to be specified according to the test antimicrobial substance and claimed microorganism under investigation. Justification should be provided for the minimum value of the PK/PD index (PK-PD target) that is aimed to predict clinical efficacy.

Regardless of which PK/PD approach is used, the overall assessment of the PK/PD relationship should be sufficiently comprehensive to assess with a reasonable confidence whether or not the test antimicrobial substance, when used at an adequate dose and interval, would show clinical efficacy against claimed target pathogens that appear to be susceptible *in vitro*.

For the purpose of PK/PD considerations a MIC value which is representative for the respective bacterial population intended to be treated (the MIC to be used for assessment of PK-PD target attainment e.g. MIC_{90}, ECOFF) should be deduced based on the target pathogen MIC distribution profile. When more than one target pathogen will be claimed for the same therapeutic indication, PD data of the least susceptible target pathogen should be considered to identify the bacterial target species which is dose limiting. In addition, further PD data such as MBC and data from time-kill studies to define the type of killing action, should be considered.

PK data are usually derived from healthy or experimentally infected target animals. As data on kinetic variability considerably increases the predictive value of the PK/PD relationship, PK data from naturally diseased animals may be collected using population kinetic models. PK data should include information on the concentration-time profile of the biologically active drug in serum/plasma and, if possible, in the biophase. The protein binding should be determined as the free (unbound) fraction is normally required to establish a PK/PD relationship.

Use of the PK/PD relationship can be made to justify the dosages to be used in dose-determination studies. In some cases where the PK/PD relationship is well established using validated approaches, it may be possible to omit dose-determination studies and to confirm the efficacy of one or a very few dose regimens in clinical trials (dose confirmation and clinical field studies). To be acceptable, justification should be provided prospectively for the eligibility of such an approach.

At present the use of the PK/PD relationship to predict the optimal duration of treatment is not well established. Thus, it should be considered whether preliminary dose regimen-finding studies are needed to identify a suitable duration of treatment for each claimed indication (for long-acting substances/formulations see section 7.2).

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 target pathogens, including multidrug resistant organisms that are rarely encountered) analysis of the PK/PD relationship may also provide important supportive information on the potential efficacy of the test antimicrobial substance.

When the PK/PD relationship is used to support the selection of a clinical breakpoint the EUCAST approach can be applied, which in addition to other data, makes use of the Monte Carlo Simulation (MCS). MCS is used to estimate exposures of the antimicrobial substance in the target animal population (population modelling) at commonly used dosing regimens. MCS can be performed by pooling available raw data in a meta-analysis, if appropriate.

7. Clinical studies

7.1. General Principles

It is recommended to conduct 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. For treatment claims, one clinical study using a negative control group should be provided preferably as a minimum, unless the superiority of the product is proven otherwise.

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 veterinary medicinal 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: treatment, metaphylaxis and prevention (for definition: see glossary). A metaphylaxis claim can only be accepted in conjunction with a treatment claim.

7.2. 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 reduce any negative impact on animal welfare. Group sizes of negative controls should be the minimum required to produce meaningful data. If acute clinical signs of disease are expected, monitoring should be focused around the peak of expected effect.

Consideration should be given to study designs that incorporate more than one of the parameters mentioned above (dose level, dosing interval, number of administrations) so as to reduce the number of negative control groups used overall in dose-determination studies. If it is not feasible to perform studies to explore different dosing strategies other data could be used as support. Regarding the dose level and the dosing interval, the PK and PD characteristics of the product should be considered to support the necessary exposure and consequently achieve a satisfactory balance between efficacy and risk for selecting for resistance. The recommended treatment duration could be justified on basis of the time course of disease progress. In addition, when available, data from published clinical studies comparing different dosing regimens for a similar product or of the same substance class with a similar activity may be used to support the need for any certain duration of exposure to the active substance. For long-acting formulations the duration of activity should be justified by reference to the time necessary to successfully combat the target bacterial infection.

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). A strain representative of the wild type population (e.g. fully susceptible towards the substance under study) could be used. However, if a claim is made for bacteria where reduced susceptibility relative to the wild type is common, 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. If this is not possible due to lack of an established experimental model, conclusive information regarding the treatment effect for the least susceptible species needs to be presented from dose

confirmation and/or clinical field studies. The validity of the experimental models used should be justified with regard to their capability to establish infection and cause a clinical disease similar to that in naturally infected animals. For treatment claims, the drug administration should normally not be initiated before the clinical signs relating to the bacterial infection are observed. However, initiation of treatment before clinical signs appear may be acceptable in case of per-acute disease, when a validated model is available that justifies this procedure.

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

When appropriate, 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. The aim is to demonstrate that the chosen dose provides sufficient efficacy without over-exposure.

Efficacy evaluation should be based on clinical and bacteriological response as determined by appropriate clinical and bacteriological assessment. Mortality should be assessed and *post mortem* data should be added wherever meaningful. The efficacy endpoints (primary and secondary) and timing of the response assessment used should be justified in relation to the disease and veterinary medicinal product under study. Observations should be collected repeatedly before, during and after treatment, as appropriate. The time of response assessment should be selected so as to show the effect of treatment in a relevant matter as compared to the negative control, thereby taking into account the effect of the treatment and the natural course of the disease.

Statistical comparisons between different treatment groups and the negative control group should be provided if possible, although it is acknowledged that dose determination studies are often not designed 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 for the veterinary medicinal product 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. For 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 in the previous section. 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.

7.3. 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. When naturally infected animals are used, infection with the relevant bacterium(a) should be confirmed through appropriate sampling procedures and susceptibility testing of isolates should be performed.

A study should preferably include a negative control group. Appropriate measures should be applied to reduce any negative impact on animal welfare. In treatment claims where 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 (CVMP/EWP/81976/2010).

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 the one(s) intended for use in the field trials.

Dose confirmation studies may allow for the assessment of relapse among animals that were considered successfully treated at the time of primary efficacy assessment. A high relapse rate could indicate that the treatment was not sufficiently effective to combat the infection. The objective is to distinguish between relapse and re-infection; therefore, if it is clinically feasible then the study design should accommodate this. It is acknowledged, however, that relapse rate assessment may be based on clinical signs and that microbiological analysis is not performed on all animals with the consequence that relapse and re-infection cases cannot always be fully separated. An appropriate assessment time point for relapse rate assessment would be after concentrations of the active substance have decreased below therapeutic concentrations in plasma or in the relevant biophase of the target tissue and the risk for including re-infected animals is still low. The time selected should be justified in this respect. (For definition of relapse and re-infection, see glossary).

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 should be presented if the dose finding is based on PK/PD relationship only.

For group/flock medication via water or feed, the variability between animals in feed/water intake should be explored through appropriate sampling of the animals, with the purpose of ensuring that the dose selected will provide therapeutic exposure levels in all animals. In addition, population PK/PD models (such as Monte Carlo simulations) based on data from field trials could be used to bring support for a post-hoc analysis of the selected dose.

7.4. Clinical field trials

7.4.1. Study design and population

Clinical 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 types and geographical location. Furthermore, the sample size should be determined according to appropriate statistical principles (CVMP guideline on statistical principles for veterinary clinical trials (CVMP/EWP/81976/2010)). Blinding of the study needs to be ensured through appropriate study design and conduct measures. This could include the use of dummy treatment, if necessary.

7.4.2. Control

Negative control

Including a placebo or an untreated control group may be of value in situations where a high self-cure rate could be suspected since the risk for erroneous conclusions is present in these situations. Negatively controlled studies can also be useful when there are no approved veterinary medicinal products for the indication in question to serve as control, and in infections with bacteria resistant to previously authorised substances. A negatively controlled study is normally necessary to support a prevention claim and in some situations also to gain support for a metaphylactic claim (see separate sections).

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 veterinary medicinal product authorised under Directive 2001/82/EC for the same indication. The applicant should pay attention to that the chosen control product is sufficiently effective for the target indication at the time the study is conducted.

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 applicants are not sure if their proposed control product would be suitable.

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 to an authorised product it has to be taken into consideration that the positive control is an effective 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 including an existing control product is a valuable means to support efficacy where the target population corresponds to clinical conditions of particular severity and where due to this there is reasons to suspect that approved products would be less effective.

7.4.3. Inclusion criteria

Clinical trials should incorporate strictly defined clinical and microbiological inclusion criteria as appropriate for the claimed indication. For all isolates collected, susceptibility of the bacteria to the test product (and to the control product) 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 through microbiological sampling performed at the time of inclusion.

If 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 of disease 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.

For products which according to official guidance should be reserved for certain situations only (i.e. for cases of treatment failure or expected failure of other substances, due to resistance or to less favourable activity characteristics) the inclusion criteria have to be considered with particular care. An appropriate study population for such products could for example be animals from herds with known history of resistance among isolates of the target pathogens towards substances that would normally have been the first treatment choice. Occurrence of resistance should in this case be confirmed through *in vitro* susceptibility tests of isolates from a relevant proportion of the animals. This study would have to include an effective positive control, implying the bacterium(a) under study is (are) fully susceptible to the chosen control. If no such product is available a negative control should be included. If full correspondence between the study population and the intended target population is not feasible, sufficient information regarding the efficacy could be obtained according to the approach outlined below (alternative approaches may also be relevant).

The effect of treatment is evaluated in two studies:
One includes a study population which does not fully correspond to the target population for treatment (e.g. the animals are not treatment failure cases but the product is used as first treatment option). This study is dimensioned to allow for a statistical confirmation of the results and the clinical relevance of the observed effect needs to be justified. Further to this, the effect of treatment is evaluated in a second study, using a smaller group of animals which fully corresponds to the target population (e.g. animals who have not responded sufficiently to previous treatment). The number of animals to be included in that study depends on the indication, the species, the expected efficacy level and the between-animal variation in treatment response. The objective is to obtain a reasonably reliable estimation of the expected treatment effect in the target population. Both studies would have to include a positive (or negative) control as outlined in the previous paragraph. It is acceptable that the number of animals included in the second study is not based on a sample size calculation that would ensure the possibility to statistically confirm the outcome of the treatment. The results of these two studies will however need to be in general agreement and any deviation will have to be justified with regard to its potential clinical significance.

Further information to support and justify the treatment can be obtained from *in vitro* data that demonstrate sufficient susceptibility of the target pathogens towards the antimicrobial substance under study and common and wide-spread resistance in Europe to other substances that would have been first priority for treatment.

In diseases characterized by mixed infections (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 proportion of the included animals to clarify which bacteria are involved in the disease process, and the *in vitro* susceptibility pattern should be tested for the most commonly occurring pathogens.

7.4.4. Exclusion criteria

Animals where the effect assessment could be biased from any previous or concomitant treatment should not be included in the study. Appropriate and justified time intervals between previous treatment and study inclusion should be applied. Any other relevant exclusion criteria, dependent on the infection to be treated, can be established. These criteria will help defining the target population in any future marketing authorisation.

7.4.5. 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.

7.4.6. Endpoints and timing of efficacy assessment

Response to therapy should be mainly based on clinical response criteria and where relevant on microbiological criteria 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 endpoint, should be the parameter capable of providing the most relevant and convincing evidence for effect from a clinical perspective, directly related to the primary objective of the trial.

Clinical cure rate following appropriate diagnostic procedures is in most situations the preferred primary endpoint. However, depending on the epidemiology and pathogenesis 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 and fish, 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.

Post-treatment follow-up should be performed to assess the risk for relapse after the effects of treatment are expected to have ceased i.e. after 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. High relapse rate may call into question the overall efficacy of the product for treatment (and metaphylaxis, if relevant), if return of clinical signs cannot be attributed to re-infection (see related comment section 7.3). The timing of the follow-up measurement should be considered carefully (see section 7.3). Bacteriological sampling and susceptibility tests from clinical failures and relapses should be performed, if feasible.

7.4.7. Special considerations for metaphylaxis claims

Outbreaks of infections may occur in a herd/unit due to the introduction and quick spread of a certain microbe that causes clinical disease in a large proportion of the stock within a short time span. A similar situation can occur when the introduction of an external factor (e.g. a virus infection) causes clinical disease due to an opportunistic bacterial infection which is harboured within the herd. For highly contagious and/or severe diseases, simultaneous treatment of clinically diseased animals and metaphylaxis of clinically healthy animals that are likely to be in the incubation phase due to close contact with diseased animals or exposed to the same external factor may be justified from an epidemiological point of view. The objective would be to control disease spread and/or 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. The need for metaphylaxis should always 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 and the severity of clinical signs) should be justified on epidemiological and clinical grounds. The justification may refer to published literature studies.

Some formulations (e.g. products to be mixed into drinking water) allow only a claim for both (treatment and metaphylaxis) as all animals will be treated independent of their individual clinical status, whereas formulations intended for individual treatment, like injectables may be approved either for only treatment or for treatment and metaphylaxis.

If 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. A metaphylaxis claim will be accepted in addition to a treatment claim, if sufficient efficacy on group level is demonstrated, and if the need for metaphylaxis can be justified for the disease.

A metaphylaxis claim can also be approved for formulations intended for individual treatment (e.g. injectables): Literature data that document the disease characteristics, epidemiology and the clinical effects of metaphylaxis may be used to support a metaphylaxis claim in this case. When literature data clearly show that effective metaphylaxis can be obtained in target disease outbreaks by use of a product which is comparable to the product under investigation (in terms of active substance, pharmaceutical form and duration of activity), it would be sufficient to confirm efficacy of treatment in a clinical trial which only includes clinically affected animals (i.e. only the treatment claim would have to be confirmed). No data from in-contact animals would have to be presented in this situation, since it will be assumed that the metaphylaxis effect level will not be less than the efficacy level in clinically affected animals.

When insufficient literature information is available to support a metaphylaxis claim for a product intended for individual treatment of group housed animals, new clinical data should be provided. When designing such clinical studies the following should be specifically considered:

- 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 and reflected in the inclusion criteria for the clinical trial protocol.
- The primary endpoint should be the clinical health status of the animals as measured by appropriate parameters.
- The duration of treatment should be carefully justified, taking into account factors such as duration of shedding of infectious organisms, development of immunity and the need to limit development of antimicrobial resistance.

- Non antimicrobial supportive treatment should be allowed in the treatment and the placebo group, if not interfering with the efficacy evaluation.
- The follow-up period should be sufficient to conclude on the efficacy for prevention of clinical disease in unaffected but treated animals.
- The study design and selected herds and houses used where any such studies are performed should assure that management or housing do not add unacceptable bias to the study results.
- All studies should include a negative control. A rescue protocol should be included in consideration of animal welfare.
- 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.

7.4.8. Special considerations for preventive claims

Preventive claims refer to individual administration of a VMP to healthy animals to prevent infection. Such claims should only be considered in those situations where the risk for infection is very high and the consequences are severe. Prevention claims are not expected to be common and will be carefully scrutinized to ensure that the intended use complies with prudent use principles. The need for prevention must be fully justified for each target species and indication.

To support a preventive claim a study including a negative control is normally 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. Alternative study designs may exceptionally be accepted provided the efficacy of the preventive treatment can be determined with sufficient certainty. The criteria used to assess the outcome of disease and/or infection should be fully described.

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

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

8. Summary of product characteristics (SPC)

The summary of product characteristics (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.

Glossary

- 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.
- Co-resistance: [Codex] The ability of a microorganism to multiply or persist in the presence of different classes of antimicrobials due to possession of various resistance mechanisms. [EFSA

2009] Genes conferring AMR are frequently contained in larger genetic elements such as integrons, transposons or plasmids, and as such may be “linked” to other, unrelated resistance genes. In such cases, multiple resistance genes may be transferred in a single event. When two or more different resistance genes are physically linked, this is termed co-resistance. Consequently, selection for one resistance attribute will also select for the other resistance gene(s), termed co-selection.

- Cross-resistance: [Codex] The ability of a microorganism to multiply or persist in the presence of other members of a particular class of antimicrobial agents or across different classes due to a shared resistance mechanism.
- Metaphylaxis: Group treatment of all clinically healthy (but presumably infected) animals kept in close contact with animals showing clinical signs of a contagious disease. Metaphylaxis is always combined with the treatment of the diseased individuals and consequently a metaphylaxis claim will only be accepted in conjunction with a treatment claim.
- Negative control: animals treated with placebo, or left untreated.
- Positive control: animals treated with an appropriate antimicrobial other than the test product.
- Prevention: administration of a VMP to healthy animals to prevent infection if the risk for infection is very high and the consequences severe.
- Re-infection: The re-occurrence of an infection in an animal which according to any relevant microbiological investigation performed after previous antimicrobial treatment was free from infection. The second period of infection could be due to a different bacterial species or strain. In the context of this guideline it is assumed that the infection occurs in conjunction with clinical signs typical for the disease under study.
- Relapse: The confirmation of an infection in an animal which after antimicrobial treatment was clinically but not bacteriologically cured from the same infection. In the context of this guideline it is assumed that the infection occurs in conjunction with clinical signs typical for the disease under study.
- Treatment: A treatment claim refers to the administration of a VMP after the onset of clinical signs of disease and only clinically affected individuals are to be treated.

References

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, as amended.

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes

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

CVMP guideline on the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99)

CVMP guideline for guidance on fixed combination products (EMEA/CVMP/83804/2005)

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

CVMP guideline on the assessment of the risk to public health 5 from antimicrobial resistance due to the use of an 6 antimicrobial veterinary medicinal product in food-producing animals – draft (EMA/CVMP/AWP/706442/2013)

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)

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

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

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