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2 EMA/CVMP/627/2001-Rev.2*
3 Committee for Veterinary Medicinal Products (CVMP)

4 **Guideline for the demonstration of efficacy for veterinary**
5 **medicinal products containing antimicrobial substances**
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8 This revision replaces the previous version of the CVMP guideline for the demonstration of efficacy for
9 veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).
10

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

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Keywords	<i>Veterinary medicinal products, antimicrobial(s), antibiotic, efficacy, antimicrobial resistance, susceptibility, treatment, metaphylaxis, prophylaxis</i>
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13 *The current revision consists of changes made in order to align the guideline to the new definitions
14 and terminology provided by Article 4 of Regulation (EU) 2019/6. In particular, the guideline has been
15 aligned with the definitions for “prophylaxis” and “metaphylaxis” and the provisions for responsible use
16 of antimicrobials stated in Articles 107(3) and 107(4) of Regulation (EU) 2019/6. The references to the
17 legislation applicable and other scientific guidelines have also been updated.

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

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54 **1. Executive summary**

55 This guideline provides recommendations for the design and conduct of pre-clinical studies and clinical
56 trials to support clinical efficacy for an antimicrobial¹ veterinary medicinal product (VMP). Appropriate
57 methods to identify and describe the pharmacology of the active substance in relation to the target
58 pathogen are presented and important aspects to consider for justifying the use of a certain active
59 substance for a particular indication are outlined. Advice regarding study design, selection of
60 comparator product and efficacy endpoints is given for the purpose of gaining conclusive study results
61 for the intended claim which could be treatment, treatment and metaphylaxis, or prophylaxis.
62 Alternative study designs may be applied if justified.

63 **2. Introduction (background)**

64 The objective of this guideline is to specify the data required to demonstrate the efficacy of a
65 veterinary medicinal product containing an antimicrobial for (a) given indication(s) using an
66 appropriate therapeutic regimen. Thus, the following sections provide guidance on the essential data
67 requirements which the applicant should cover in order to demonstrate efficacy, i.e. pre-clinical studies
68 (pharmacokinetics (PK), pharmacodynamics (PD) including antimicrobial resistance mechanisms, dose
69 determination and dose confirmation studies) and clinical trials.

70 **3. Scope**

71 This guideline applies to all veterinary medicinal products containing antimicrobial substances and
72 intended only to treat or prevent infections (within the boundaries of the uses permitted under
73 Regulation (EU) 2019/6). The content thereof covers all pharmaceutical forms, all routes of
74 administration and all target animal species.

75 This guideline has been developed primarily for antibiotics but could be applied to other types of
76 antimicrobial substances included in veterinary medicines. For complementary information, other CVMP
77 and VICH guidelines should be read in conjunction with this guideline, such as the CVMP guideline for
78 the demonstration of efficacy for veterinary medicinal products containing anticoccidial substances
79 (EMA/CVMP/EWP/755916/2016).

80 For antimicrobials intended for intramammary administration, the CVMP guideline on the conduct of
81 efficacy studies for intramammary products for use in cattle (EMA/CVMP/344/1999) should also be
82 considered.

83 Cross-reference is also made to the CVMP guideline on the conduct of pharmacokinetic studies in
84 target animal species (EMA/CVMP/133/1999).

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

87 The VICH GL27: Guidance on pre-approval information for registration of new veterinary medicinal
88 products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01) and
89 the CVMP guideline on the assessment of the risk to public health from antimicrobial resistance due to
90 the use of an antimicrobial veterinary medicinal product in food producing animals
91 (EMA/CVMP/AWP/706442/2013) can also be considered for the development of antimicrobials.

¹ Antimicrobial: any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.

92 This guideline applies to all applications where, according to Regulation (EU) 2019/6, new data has to
93 be generated to support clinical efficacy.

94 **4. Legal basis**

95 This revision replaces the previous version of the CVMP guideline for the demonstration of efficacy for
96 veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1) and
97 should be read in conjunction with Regulation (EU) 2019/6.

98 In accordance with Annex II of Regulation (EU) 2019/6, all experiments on animals should be
99 conducted taking into account the 3Rs principles (replacement, reduction and refinement) as laid down
100 in Directive 2010/63/EU on protection of animals used for scientific purposes.

101 Applicants should also refer to other relevant European and VICH guidelines, including those listed in
102 the reference list of this document.

103 **5. General considerations**

104 Antimicrobials including antibiotics, antivirals, antifungals and anti-protozoals are powerful and
105 important tools to combat microbial infections in animals. In order to minimise the potential selection
106 for antimicrobial resistance and thereby to prolong the time period during which the substance will
107 remain effective, it is vital that all unnecessary or inadequate use is avoided. In addition, potential
108 risks to public health need to be considered for example as outlined in separate guidelines (VICH GL27
109 and EMA/CVMP/AWP/706442/2013).

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

- 112 • The indication should be justified. Use of antimicrobials for treatment of mild and transient
113 infections that will resolve independent of treatment will be questioned. In case of multi-factorial
114 diseases, efforts should be made to describe the expected contribution from the antimicrobial
115 treatment, e.g. through appropriate reference to published information, and studies should be
116 designed considering where and when there is a place for an antimicrobial in the treatment
117 strategy.
- 118 • The target population for therapy should be well defined and possible to identify under field
119 conditions. The study population in clinical trials should reflect the intended target population for
120 therapy to the best possible extent.
- 121 • Official guidance and CVMP recommendations² (e.g. EMA/CVMP/CHMP/682198/2017) should be
122 considered, with an intention to obtain the best achievable alignment between the study
123 population and the target population for treatment. Any deviation from official guidance
124 recommendations should be justified.
- 125 • The dose and the dosing interval of the antimicrobial product can be justified by considering the
126 pharmacodynamic/pharmacokinetic (PK/PD) relationship, if established, as well as the severity of
127 the disease, whereas the number of administrations should be in line with the nature of the
128 disease. To avoid unnecessary exposure to antimicrobials (and thus unnecessary selection

² <https://www.ema.europa.eu/en/veterinary-regulatory/research-development/scientific-guidelines/safety-residues/safety-residues-antimicrobials> and [Antimicrobial resistance in veterinary medicine | European Medicines Agency \(europa.eu\)](#)

129 pressure for resistant pathogens), the duration of exposure should not be longer than necessary
130 to accomplish the desired outcome.

131 Principally there are three different kinds of claims: treatment, metaphylaxis and prophylaxis (for
132 definition: see glossary). A metaphylaxis claim can only be accepted in conjunction with a treatment
133 claim.

134 **6. Pre-clinical studies**

135 In the context of this section, the focus is principally on antibiotics but may, on a case-by-case basis,
136 also be applicable to other antimicrobials if relevant.

137 It is recommended that pre-clinical efficacy studies should follow the requirements for Good Clinical
138 Practice (GCP) and/or Good Laboratory Practice (GLP), as appropriate (depending on the nature of the
139 studies). In case GCP and/or GLP is not applied (e.g. absence of certified GLP status), traceability,
140 accuracy, integrity and correctness of data should be ensured, and the use of such data in pivotal
141 studies should be justified.

142 **6.1. Pharmacology**

143 The pharmacokinetic and pharmacodynamic properties of the active substance should be adequately
144 documented.

145 For the conduct of pharmacokinetic studies please refer to the CVMP guideline on conduct of
146 pharmacokinetic studies in target animal species (EMA/CVMP/133/1999). Sufficient pharmacokinetic
147 data should be provided to support the dose regimen and route of administration for the intended
148 authorisation. Where applicable, pharmacokinetic data for the relevant biophase (target site of effect of
149 the substance) should also be supplied for the purposes of determining the PK/PD relationship (see
150 section 6.7). Studies on pharmacodynamics should be performed according to validated and
151 internationally accepted methods, and according to Good Laboratory Practice (GLP), when applicable.
152 Data requirements are detailed below.

153 **6.1.1. Antimicrobial class**

154 The antimicrobial class should be stated.

155 **6.1.2. Mode and mechanism of action**

156 The mode and mechanism of action of the antimicrobial substance on the target pathogen should be
157 reported.

158 The spectrum of the antimicrobial activity of the substance should be defined. Intrinsically resistant
159 microorganisms which may also be associated with disease relevant to the intended use of the
160 veterinary medicinal product should be reported.

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

164 **6.1.3. Minimum Inhibitory Concentration (MIC)**

165 The minimum inhibitory concentration (MIC) is the lowest concentration (expressed in µg/ml or mg/l)
166 of an antimicrobial substance which, under defined *in vitro* conditions, prevents the visible growth of

167 microbes. MIC values should be determined using accepted standardised methodology, preferably such
168 as described by EUCAST³ and, if not available, as in CLSI⁴ documents. Dilution methods, when
169 available, should be used and the methods clearly described. However, it is recognised that to date
170 standardised methodologies are not available for all organisms.

171 MIC data should be provided for all target pathogens (primarily bacteria, but other microorganisms as
172 well, for which internationally recognised methods for MICs testing are available). A scientifically
173 justified number of clinical isolates of each target pathogen, representative of the EU area, should be
174 collected to allow detection of isolates with MICs deviating from the normal distribution of isolates
175 without any acquired resistance (wild type). For rare pathogens a lower number of isolates could be
176 justified than for commonly encountered pathogens. The isolates of the target pathogens to be tested
177 should have been collected within five years prior to the submission of the application. Isolates should
178 be epidemiologically unrelated (not coming from the same episode of disease in the same herd or
179 same animals). For target pathogens isolated from food-producing animals, selection of livestock farms
180 should include, where applicable, units of different production types. In these cases, the tested isolates
181 should preferably come from the animal subgroup(s) or production type(s) that reflect the target
182 population for the indication. The origin of the isolates investigated (animal species, clinical condition,
183 production type, geographic area) and dates of collection should be stated.

184 The susceptibility to antimicrobial substances varies not only between different species of
185 microorganisms, but also between strains and over time. The complete MIC distribution data for all
186 isolates tested of each microorganism should be reported in tables and if relevant, divided by origin as
187 indicated above. In case the MIC distribution indicates the presence of subpopulations of bacteria with
188 reduced susceptibility (bi- or multimodal distribution), these should be compared with already available
189 (historical) data to allow conclusions to be drawn on mechanisms for acquired resistance. Based on
190 these conclusions and supportive clinical data, the subpopulation with reduced susceptibility may be
191 included in the intended population to be treated. It is acknowledged that for historical data
192 information on the full MIC distribution may not be available or studies may not have been performed
193 according to the same methodology or interpreted using current interpretative criteria. In such cases
194 all available data such as MIC₅₀ and MIC₉₀ should be provided.

195 The data on MIC distribution should be interpreted using adequate interpretation criteria. The
196 epidemiological cut-off value⁵ should be provided, if feasible, to define the population without any
197 acquired resistance. Ideally a clinical breakpoint should be proposed by the applicant. This could be
198 either the epidemiological cut-off value or a clinical breakpoint deviating from the epidemiological cut-
199 off value (i.e. a MIC value under which the selected dose regimen is shown to be effective). Any clinical
200 breakpoint should be supported by microbiological, clinical and available PK/PD data. In case reference
201 is made to a clinical breakpoint established by an external institute or published in literature from
202 peer-reviewed journals, acceptance will depend on the availability of an adequate level of detail to
203 determine if the breakpoint was appropriately characterised. It should also be demonstrated that this
204 value is relevant for the active substance in the formulation under study.

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

³ EUCAST - European Committee on Antimicrobial Susceptibility Testing

⁴ CLSI - Clinical and Laboratory Standards Institute

⁵ For definitions of epidemiological cut-off values and clinical breakpoints, please refer to EUCAST.
<http://www.srga.org/Eucastwt/eucastdefinitions.htm>

207 **6.1.4. Minimum Bactericidal Concentration (MBC) and kinetics of bacterial**
208 **killing**

209 Minimum Bactericidal Concentration (MBC) is the lowest concentration of an antibiotic (expressed in
210 µg/ml or mg/l) which, under defined *in vitro* conditions, reduces bacterial counts by 99.9%.

211 Data on the kinetics of bacterial killing should be provided to characterise the action of the antibiotic
212 against the target bacteria and to demonstrate whether its activity is bacteriostatic or bactericidal and
213 whether it is time-dependent (i.e. dependent upon the period of time during which the concentration of
214 the antibiotic exceeds the MIC, but for which concentrations of several magnitudes of the MIC do not
215 increase efficacy), concentration dependent (i.e. efficacy increases when administered at doses which
216 confer concentrations several times the MIC) or co-dependent (i.e. which depends both upon
217 concentrations above the MIC and the period of time during which the concentration of the antibiotic
218 exceeds the MIC).

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

226 **6.1.5. Antimicrobial resistance**

227 For all antimicrobial products, the potential development of antimicrobial resistance needs to be
228 addressed as outlined in Annex II to Regulation (EU) 2019/6.

229 Information on current resistance and on the potential emergence of resistance of clinical relevance for
230 the claimed indication and target pathogens in the target animal species shall be provided.

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

236 Whenever relevant, information on co-resistance and cross-resistance shall be presented, notably for
237 those isolates with MICs deviating from the normal distribution for a certain antimicrobial class.

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

240 For applications for generic veterinary medicinal products containing antimicrobial substances,
241 information about the level of resistance, as known from bibliographic data, shall be provided.

242 **6.1.6. Additional *in vitro* susceptibility studies**

243 Additional *in vitro* susceptibility studies should, whenever relevant, include an investigation of possible
244 synergy or antagonism and may include, for example, investigation of post-antibiotic effects and, for
245 certain antibiotics, an estimate of the rate of selection of resistant mutants and how concentrations
246 above the MIC may affect or prevent selection of mutants. The methods for additional susceptibility
247 studies should be well described and the clinical relevance of the obtained results should be justified.

248 Some environmental factors (e.g. pH, O₂, inhibitors, cation concentration) may influence the
249 antimicrobial activity at certain sites of infection and in biological fluids. When available and if relevant
250 to the proposed indications for use of the antimicrobial substance, these data should be reported. The
251 clinical relevance of the environmental factors should be discussed.

252 Notwithstanding the guidance on the conduct of MIC, MBC and time-kill studies presented in sections
253 6.1.3 and 6.1.4 of this guideline, namely to use internationally recommended guidelines and
254 methodology in *in vitro* studies, any differences between artificial growth matrices (as required for use
255 in international guidelines) and biological fluids, such as serum or heat-treated serum, should be
256 reported for at least a limited number of isolates.

257 **6.1.7. The pharmacokinetic/pharmacodynamic (PK/PD) relationship**

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

267 To establish doses for evaluation in clinical trials, use of PK/PD integration approaches (integrating of a
268 PD parameter with one or more PK parameters generated in a separate PK study to predict an effective
269 dose) and/or PK/PD modelling approaches (*in silico* modelling of PD and PK data generated in the same
270 study to select optimal dosage schedules) can be made. Currently the most common integration
271 approaches use PK/PD indices such as C_{max}/MIC (maximum concentration in serum or plasma/MIC),
272 %T > MIC (fraction of time during which the concentration exceeds the MIC) and AUC/MIC, by
273 convention referred to as AUIC (area under the inhibitory curve), to express a PK/PD relationship. If
274 use is made of PK/PD indices, the choice of the PK/PD index considered as best predictive of efficacy
275 should be justified. Further characterisation of PK/PD indices needs to be specified according to the
276 test antimicrobial substance and claimed target pathogens under investigation. Justification should be
277 provided for the minimum value of the PK/PD index (PK-PD target) that is aimed to predict clinical
278 efficacy.

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

283 For the purpose of PK/PD considerations a MIC value which is representative for the respective
284 bacterial population intended to be treated (the MIC to be used for assessment of PK-PD target
285 attainment e.g. MIC₉₀, ECOFF) should be deduced based on the target pathogen MIC distribution
286 profile. When more than one target pathogen will be claimed for the same therapeutic indication, PD
287 data of the least susceptible target pathogen should be considered to identify the bacterial target
288 species which is dose limiting. In addition, further PD data such as MBC and data from time-kill studies
289 to define the type of killing action, should be considered.

290 PK data are usually derived from healthy or experimentally infected target animals. As data on kinetic
291 variability considerably increases the predictive value of the PK/PD relationship, PK data from naturally
292 diseased animals may be collected using population kinetic models. PK data should include information

293 on the concentration-time profile of the biologically active drug in serum/plasma and, if possible, in the
294 biophase. The protein binding should be determined as the free (unbound) fraction is normally required
295 to establish a PK/PD relationship.

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

301 At present the use of the PK/PD relationship to predict the optimal duration of treatment is not well
302 established. Thus, it should be considered whether preliminary dose determination studies are needed
303 to identify a suitable duration of treatment for each claimed indication (for long-acting
304 substances/formulations see section 6.2.2).

305 In circumstances in which it is not feasible to generate extensive clinical efficacy data (e.g. in rare
306 types of infections or against rare types of target pathogens, including multidrug resistant organisms
307 that are rarely encountered) analysis of the PK/PD relationship may also provide important supportive
308 information on the potential efficacy of the test antimicrobial substance.

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

314 **6.2. Dose determination and dose confirmation studies**

315 **6.2.1. General principles**

316 Appropriate data shall be provided to justify the proposed dose, dosing interval, and duration of
317 treatment. All studies should be controlled and the choice of control should be justified.

318 Appropriate statistical methods should be used (see CVMP guideline on statistical principles for clinical
319 trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)).

320 The formulation of the veterinary medicinal product used for dose determination and dose confirmation
321 studies should be the final formulation proposed for authorisation. Any deviation in the formulation
322 used for these studies compared to the final product formulation should be justified.

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

325 **6.2.2. Dose determination studies**

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

330 Dose determination studies should always include a negative control. Appropriate measures should be
331 applied to reduce any negative impact on animal welfare. Group sizes of negative controls should be
332 the minimum required to produce meaningful data. If acute clinical signs of disease are expected,
333 monitoring should be focused around the peak of expected effect.

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

346 Where possible, experimentally induced infections should be used in the dose determination studies.
347 The origin and *in vitro* susceptibility of the strains used in the study should be presented (see section
348 6.1.3). A strain representative of the wild type population (e.g. fully susceptible towards the substance
349 under study) could be used. However, if a claim is made for pathogens where reduced susceptibility
350 relative to the wild type is common, this should be taken into account when selecting the test strain. In
351 case several target pathogens will be included in the sought indication (e.g. bovine respiratory disease)
352 dose determination should be based on the least susceptible species as evident from relevant data. If
353 this is not possible due to lack of an established experimental model, conclusive information regarding
354 the treatment effect for the least susceptible species needs to be presented from dose confirmation
355 studies and/or clinical trials. The validity of the experimental models used should be justified with
356 regard to their capability to establish infection and cause a clinical disease similar to that in naturally
357 infected animals.

358 For treatment claims, the product administration should be initiated after the onset of disease (clinical
359 or sub-clinical). Initiation of treatment before clinical signs may be acceptable in case of a per-acute
360 disease, when a validated model is available that justifies this procedure.

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

363 When appropriate, it is recommended to include PK data in dose determination studies to allow the
364 recorded effects to be related not only to dose but more specifically to time-concentration curves
365 during treatments.

366 Usually, three levels of dosage of the veterinary medicinal product should be tested, preferably using
367 the final formulation. The aim is to demonstrate that the chosen dose provides sufficient efficacy
368 without over-exposure.

369 Efficacy evaluation should be based on clinical outcome and target pathogen response as determined
370 by appropriate clinical assessment and pathogen monitoring (e.g. isolation of the strain and, where
371 appropriate, determination of colony-forming units). Mortality should be assessed and *post mortem*
372 data should be added wherever meaningful. The efficacy endpoints (primary and secondary) and
373 timing of the response assessment used should be justified in relation to the disease and the
374 veterinary medicinal product under study. Observations should be collected repeatedly before, during
375 and after treatment, as appropriate. The time of response assessment should be selected so as to
376 show the effect of treatment in a relevant matter as compared to the negative control, thereby taking
377 into account the effect of the treatment and the natural course of the disease.

378 Statistical comparisons between different treatment groups and the negative control group should be
379 provided if possible, although it is acknowledged that dose determination studies are often not

380 designed to generate statistical support and thus conclusions are often based on descriptive
381 information.

382 From the results of dose determination studies, the applicant could decide upon an appropriate dose
383 regimen for the veterinary medicinal product which should be pursued in dose confirmation studies and
384 subsequent clinical trials.

385 **Locally acting products**

386 The dosing regimen should be substantiated also for locally active products. For formulations applied
387 directly to the infection site and which do not undergo significant dilution, a justification can be
388 sufficient, taking into account the product strength, the formulation and *in vitro* susceptibility data for
389 the target pathogen. In other cases, such as e.g. locally active products for the gastro-intestinal tract,
390 dose determination studies should be performed as detailed in the previous section. Notably, the
391 extent of systemic absorptions is one aspect limiting the upper dose for a locally active compound. For
392 details on intramammary products, please see the CVMP guideline for the conduct of efficacy studies
393 for intramammary products for use in cattle (EMA/CVMP/344/1999). Regarding systemically
394 administered products intended to combat a localised infection (e.g. metritis) the dose should be
395 established according to recommendations given in the previous section.

396 **6.2.3. Dose confirmation studies**

397 The aim of dose confirmation studies is to confirm the efficacy of the selected dosage regimen under
398 controlled clinical conditions. These studies can be performed using experimental models of infections
399 but well controlled studies using naturally infected animals are preferred. When naturally infected
400 animals are used, infection with the relevant target pathogen should be confirmed through appropriate
401 sampling and identification procedures, and susceptibility testing of isolates should be performed.

402 A study should preferably include a negative control group. Appropriate measures should be applied to
403 reduce any negative impact on animal welfare. In treatment claims where the use of a negative control
404 is not possible, an appropriate positive control may be acceptable provided internal validity and
405 sensitivity of the study is ensured (CVMP/EWP/81976/2010).

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

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

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

- 422 • the conditions of the dose determination studies are representative of the field conditions in terms
423 of the type of infection and the animals involved,

- 424 • the susceptibility pattern for any challenge strain used for dose determination is relevant for the
425 field situation,
426 • a clear dose-effect relationship is documented as supported by adequate dose determination data,
427 • the dose determination data allows for the selection of one appropriate dose level,
428 • the dosing interval and the number of administrations is adequately justified.

429 At least one dose confirmation study should be presented if the dose determination is based on PK/PD
430 relationship only.

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

436 Where dose confirmation studies have been conducted under field conditions, relevant information
437 should be provided under 'clinical trials' (see section 7, below).

438 **7. Clinical trials**

439 **7.1. General principles**

440 Clinical trials shall be conducted in accordance with established principles of good clinical practice
441 (GCP), unless otherwise justified.

442 Unless otherwise justified, clinical trials shall be carried out with control animals (controlled clinical
443 trials). The choice of control should be justified.

444 Clinical trials should cover each proposed indication and pathogen species in each target animal
445 species claimed. The number of clinical trials will depend on the type of veterinary medicinal product
446 and nature of the disease, and also on the size and quality of studies conducted.

447 Appropriate statistical methods should be used (see CVMP guideline on statistical principles for clinical
448 trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)).

449 The final formulation of the veterinary medicinal product should be used. If the formulation used in the
450 clinical trials differs from the final formulation, the relative bioavailability should be documented.

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

453 **7.2. Study design and population**

454 Clinical trials should be multicentric, randomised, blinded and controlled, and conducted in naturally
455 infected animals. For a given indication, the study population should be well defined, and
456 representative of the intended target population for therapy. This includes considerations regarding
457 housing conditions, production types and geographical location. Furthermore, the sample size should
458 be determined according to appropriate statistical principles (CVMP guideline on statistical principles
459 for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)).
460 Blinding of the study needs to be ensured through appropriate study design and conduct measures.
461 This could include the use of dummy treatment, if necessary.

462 **7.3. Control**

463 **Negative control**

464 Including a placebo or an untreated control group may be of value in situations where a high self-cure
465 rate could be suspected since the risk for erroneous conclusions is present in these situations.

466 Negatively controlled studies can also be useful when there are no approved veterinary medicinal
467 products for the indication in question to serve as control, and in infections with pathogens resistant to
468 previously authorised substances. A negatively controlled study is normally necessary to support a
469 claim for prophylaxis and in some situations also to support a claim for metaphylaxis (see separate
470 sections).

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

473 **Positive control**

474 A positive control should be an authorised veterinary medicinal product that has demonstrated an
475 acceptable level of efficacy and has been approved in the EU for the proposed indication(s) for use in
476 the same target animal species. The applicant should pay attention to ensure that the chosen control
477 product is sufficiently effective for the target indication at the time the study is conducted.

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

482 Since it is of vital importance that the positive control is appropriate it is recommended that advice is
483 sought from the authorities if applicants are not sure if their proposed control product would be
484 suitable.

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

491 In case the aim is to demonstrate superiority to an authorised product it has to be taken into
492 consideration that the positive control is an effective treatment alternative for the current indication at
493 the time of investigation (see above). This would include the presentation of susceptibility data for the
494 control to ensure that any difference is not dependent on resistance development.

495 A superiority trial including an existing control product is a valuable means to support efficacy where
496 the target population corresponds to clinical conditions of particular severity and where due to this
497 there is reasons to suspect that approved products would be less effective.

498 **7.4. Inclusion criteria**

499 Clinical trials should incorporate strictly defined clinical and microbiological inclusion criteria as
500 appropriate for the claimed indication. For all isolates collected, susceptibility of the pathogens to the
501 test product (and to the control product) should be tested *in vitro*.

502 When the aim is to confirm efficacy against one or several specified pathogens, isolation of the target
503 pathogen(s) from the animals or a representative proportion of them is required through
504 microbiological sampling performed at the time of inclusion.

505 If individual sampling for target pathogens of all included animals is not feasible (e.g. herd treatment),
506 the sample size should be large enough to allow confirmation of the aetiological diagnosis with
507 sufficient level of certainty. For those animals which are included on basis of clinical signs of disease
508 only, the causal relationship to the target bacterium should be made evident through appropriate
509 clinical diagnostic criteria.

510 The microbiological sampling technique used on all or a proportion of the study animals should be
511 justified and valid in the sense that it accurately reflects the infectious status of the animal (see also
512 section 6.1.4).

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

516 For products which according to official guidance should be reserved for certain situations only (i.e. for
517 cases of treatment failure or expected failure of other substances, due to resistance or to less
518 favourable activity characteristics), the inclusion criteria have to be considered with particular care. An
519 appropriate study population for such products could for example be animals from herds with a known
520 history of resistance among isolates of the target pathogens towards substances that would normally
521 have been the first treatment choice. Occurrence of resistance should in this case be confirmed
522 through *in vitro* susceptibility tests of isolates from a relevant proportion of the animals. This study
523 would have to include an effective positive control, implying the pathogen(s) under study is (are) fully
524 susceptible to the chosen control. If no such product is available, a negative control should be
525 included.

526 If full correspondence between the study population and the intended target population is not feasible,
527 sufficient information regarding the efficacy could be obtained according to the approach outlined
528 below (alternative approaches may also be relevant).

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

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

547 In diseases characterised by mixed infections (e.g. metritis), inclusion may be based mainly on clinical
548 signs. However, to support the clinical diagnosis samples should be collected from the animals or a
549 relevant proportion of the included animals to clarify which pathogens are involved in the disease
550 process, and the *in vitro* susceptibility pattern should be tested for the most commonly occurring
551 pathogens.

552 **7.5. Exclusion criteria**

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

558 **7.6. Concomitant diseases**

559 Information on any concomitant infection and treatment should be provided where appropriate, so that
560 the impact of these potential confounding factors on the trial results can be evaluated.

561 **7.7. Endpoints and timing of efficacy assessment**

562 Response to therapy should be mainly based on clinical response criteria and where relevant on
563 microbiological criteria for the specific disease under study. The time points and methods to assess the
564 effects of treatment in clinical trials should be explained and justified.

565 The choice of the clinical endpoint is critical and determines the study design. The primary endpoint
566 should be the parameter capable of providing the most relevant and convincing evidence for effect
567 from a clinical perspective, directly related to the primary objective of the trial.

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

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

576 Post-treatment follow-up should be performed to assess the risk for relapse after the effects of
577 treatment are expected to have ceased i.e. after sub-therapeutic concentrations have been reached in
578 plasma or target tissue. Clinical failures identified at time of primary effect assessment and at time of
579 post-treatment follow-up should be addressed in detail. High relapse rate may call into question the
580 overall efficacy of the product for treatment (and metaphylaxis, if relevant), if return of clinical signs
581 cannot be attributed to re-infection (see related comment section 6.2.3). The timing of the follow-up
582 measurement should be considered carefully (see section 6.2.3). Sampling for pathogen identification
583 and susceptibility tests from clinical failures and relapses should be performed, if feasible.

584 **7.8. Special considerations for metaphylaxis claims**

585 The use of antimicrobials for metaphylaxis is only permitted in the conditions laid down in Article
586 107(4) of Regulation (EU) 2019/6, *i.e.* when the risk of spread of an infection or of an infectious
587 disease in a group of animals is high and where no appropriate alternatives are available.

588 Outbreaks of infections may occur in a herd/unit due to the introduction and quick spread of a certain
589 pathogen that causes clinical disease in a large proportion of the stock within a short time span. A
590 similar situation can occur when the introduction of an external factor (e.g. a virus infection) causes
591 clinical disease due to an opportunistic bacterial infection which is harboured within the herd.
592 Therefore, metaphylaxis (see glossary) may be justified from an epidemiological point of view. The
593 objective would be to treat the clinically sick animals and control the spread of the disease to animals
594 in close contact and at risk and which may already be subclinically infected.

595 A metaphylaxis claim is only accepted in conjunction with a treatment claim and never as a separate
596 indication. The need for metaphylaxis should always be adequately justified in the dossier and the
597 threshold for the initiation of metaphylaxis (e.g. the proportion of clinically diseased animals at a
598 certain time point within a group and the severity of clinical signs) should be justified on
599 epidemiological and clinical grounds. The justification may refer to published literature studies.

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

604 If the study formulation is to be used for group/flock administration only (such as oral powders for
605 drinking water), standard principles for study design will be applicable (see above) using relevant
606 efficacy endpoints to document treatment success. A metaphylaxis claim will be accepted in addition to
607 a treatment claim, if sufficient efficacy on group level is demonstrated, and if the need for
608 metaphylaxis can be justified for the disease.

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

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

- 622 • The threshold for the initiation of metaphylaxis (e.g. the proportion of clinically diseased animals
623 at a certain time point within a group) should be justified and reflected in the inclusion criteria for
624 the clinical trial protocol.
- 625 • The primary endpoint should be the clinical health status of the animals as measured by
626 appropriate parameters.

- 627 • The duration of treatment should be carefully justified, taking into account factors such as
628 duration of shedding of infectious organisms, development of immunity and the need to limit
629 development of antimicrobial resistance.
- 630 • Non antimicrobial supportive treatment should be allowed in the treatment and the placebo group,
631 if not interfering with the efficacy evaluation.
- 632 • The follow-up period should be sufficient to conclude on the efficacy for prevention of clinical
633 disease in unaffected but treated animals.
- 634 • The study design and selected herds and houses used where any such studies are performed
635 should assure that management or housing do not add unacceptable bias to the study results.
- 636 • All trials should include a negative control. A rescue protocol should be included in consideration of
637 animal welfare.
- 638 • The effect of metaphylaxis and treatment may be documented in the same trial. If so, efficacy
639 must be recorded on individual level and treatment outcome should be presented separately for
640 the two groups (clinically diseased animals and animals with no clinical signs but at risk of
641 developing clinical disease). In case the treatment effect is evaluated through comparison with an
642 authorized product, a negative group needs to be included to evaluate efficacy regarding the
643 metaphylaxis.

644 **7.9. Special considerations for prophylaxis claims**

645 The use of antimicrobials for prophylaxis is only allowed in the conditions laid down in Article 107(3) of
646 Regulation (EU) 2019/6, *i.e.* in exceptional cases, for the administration to an individual animal (for
647 antibiotics) or a restricted number of animals (for antimicrobials other than antibiotics) when the risk
648 of an infection or of an infectious disease is very high and the consequences are likely to be severe.

649 The need for prophylaxis must be fully justified for each target species and indication.

650 To support a prophylaxis claim, a study including a negative control is normally needed and animal
651 welfare should be accounted for through the acceptance of adequate supportive treatment in both test
652 and control group and implementation of rescue protocols. Alternative study designs may exceptionally
653 be accepted provided the efficacy of the prophylaxis can be determined with sufficient certainty. The
654 criteria used to assess the outcome of disease and/or infection should be fully described.

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

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

659 **8. Summary of product characteristics (SPC)**

660 The summary of product characteristics (SPC) for veterinary medicinal products containing
661 antimicrobial substances should contain the information laid down in Article 35 of Regulation (EU)
662 2019/6.

663 In addition, specific guidance to be considered by applicants is included in the CVMP guideline on the
664 summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial
665 substances (EMA/CVMP/383441/2005) and the Questions and answers on the guideline on the SPC for
666 VMPs containing antimicrobial substances – antibiotic clinical breakpoints that may be included in
667 section 4.2 of the SPC for generic VMPs (EMA/CVMP/AWP/933465/2022).

668 Recommendations presented by CVMP for different classes of antimicrobials, such as reflection papers
669 or advice on AMEG categorisations, should also be considered; outcomes from previous referrals
670 should also be taken into account when preparing the SPC for VMPs containing antimicrobial
671 substances.

672 Definitions

- 673 • **Antibiotic:** Any substance with a direct action on bacteria that is used for treatment or prevention
674 of infections or infectious diseases (see Article 4(14) of Regulation (EU) 2019/6).
- 675 • **Antimicrobial:** Any substance with a direct action on micro-organisms used for treatment or
676 prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and
677 anti-protozoals (see Article 4(12) of Regulation (EU) 2019/6).
- 678 • **Antimicrobial resistance:** The ability of micro-organisms to survive or to grow in the presence
679 of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-
680 organisms of the same species (see Article 4(11) of Regulation (EU) 2019/6).
- 681 • **Clinical trial:** A study which aims to examine under field conditions the safety or efficacy of a
682 veterinary medicinal product under normal conditions of animal husbandry or as part of normal
683 veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof
684 (see Article 4(17) of Regulation (EU) 2019/6).
- 685 • **Co-resistance:** In the context of this guideline, "co-resistance" means the presence of resistance
686 to more than one class of antimicrobial in the same bacterial strain, as might occur when different
687 resistance genes are found on the same plasmid.
- 688 • **Co-selection of resistance:** In the context of this guideline, "co-selection of resistance" means
689 the selection of multiple AMR genes when one of these is selected by the presence of a relevant
690 antimicrobial. An example of this is the integron, which may carry a gene cassette(s) encoding
691 AMR genes that is (are) under the control of a single promoter. As a result, these genes are
692 expressed in a coordinated manner, although the furthest downstream gene may not be as
693 efficiently expressed as the gene next to the promoter. These cassettes are commonly found in
694 both Gram-positive and Gram-negative bacteria. They can become a part of the bacterial
695 chromosome or plasmid and can then be transmitted amongst different bacterial strains.
- 696 • **Cross-resistance:** In the context of this guideline, "cross-resistance" means that a single
697 resistance mechanism confers resistance to an almost entire class of antimicrobials. An example is
698 the aminoglycoside-modifying enzymes which may confer resistance to several members of the
699 aminoglycoside family. Cross resistance can occur across different classes of agents - a result of
700 either overlapping drug targets, as is the case with macrolides and lincosamides, or a drug efflux
701 pump with a broad range of activity (i.e. capable of exporting different classes of drugs).
- 702 • **Metaphylaxis:** The administration of a medicinal product to a group of animals after a diagnosis
703 of clinical disease in part of the group has been established, with the aim of treating the clinically
704 sick animals and controlling the spread of the disease to animals in close contact and at risk and
705 which may already be subclinically infected (see Article 4(15) of Regulation (EU) 2019/6).
- 706 • **Pre-clinical study:** A study not covered by the definition of clinical trial which aims to investigate
707 the safety or efficacy of a veterinary medicinal product for the purpose of obtaining a marketing
708 authorisation or a change thereof (see Article 4(18) of Regulation (EU) 2019/6).
- 709 • **Prophylaxis:** The administration of a medicinal product to an animal or group of animals before
710 clinical signs of a disease, in order to prevent the occurrence of disease or infection (see Article
711 4(16) of Regulation (EU) 2019/6).
- 712 • **Re-infection:** In the context of this guideline, "re-infection" means the re-occurrence of an
713 infection in an animal which according to any relevant microbiological investigation performed
714 after previous antimicrobial treatment was free from infection. The second period of infection

715 could be due to a different bacterial species or strain. In the context of this guideline it is assumed
716 that the infection occurs in conjunction with clinical signs typical for the disease under study.

717 • **Relapse:** In the context of this guideline, “relapse” means the re-occurrence of an
718 infection/disease during the follow-up observation period with isolation of the same causative
719 pathogen in an animal which was considered successfully treated after the end of the antimicrobial
720 treatment. It is assumed that the infection occurs in conjunction with clinical signs typical for the
721 disease under study.

722 • **Treatment:** In the context of this guideline, “treatment” means the administration of an
723 antimicrobial veterinary medicinal product after the onset of a disease (clinical or sub-clinical) for
724 curative purposes.

725

726 **References**

- 727 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on
728 veterinary medicinal products and repealing Directive 2001/82/EC
- 729 Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the
730 protection of animals used for scientific purposes
- 731 Categorisation of antibiotics in the European Union - Answer to the request from the European
732 Commission for updating the scientific advice on the impact on public health and animal health of the
733 use of antibiotics in animals (EMA/CVMP/CHMP/682198/2017)
- 734 CVMP guideline for the demonstration of efficacy for veterinary medicinal products containing
735 anticoccidial substances (EMA/CVMP/EWP/755916/2016)
- 736 CVMP guideline for the conduct of efficacy studies for intramammary products for use in cattle
737 (EMA/CVMP/344/1999)
- 738 CVMP guideline on the conduct of pharmacokinetic studies in target animal species
739 (EMA/CVMP/133/1999)
- 740 CVMP guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005)
- 741 CVMP guideline on statistical principles for clinical trials for veterinary medicinal products
742 (pharmaceuticals) (EMA/CVMP/EWP/81976/2010)
- 743 CVMP guideline on the assessment of the risk to public health from antimicrobial resistance due to the
744 use of an antimicrobial veterinary medicinal product in food-producing animals
745 (EMA/CVMP/AWP/706442/2013)
- 746 CVMP guideline on the summary of product characteristics (SPC) for veterinary medicinal products
747 containing antimicrobial substances (EMA/CVMP/383441/2005)
- 748 CVMP Questions and answers on the guideline on the SPC for VMPs containing antimicrobial substances
749 – antibiotic clinical breakpoints that may be included in section 4.2 of the SPC for generic VMPs
750 (EMA/CVMP/AWP/933465/2022)
- 751 CVMP Question and answer document on requirements for pre-clinical studies submitted in support of
752 a marketing authorisation application for a veterinary medicinal product (EMA/CVMP/565615/2021)
- 753 CVMP strategy on antimicrobials 2021-2025 (EMA/CVMP/179874/2020)
- 754 Good Laboratory Practice (GLP) (see Directive 2004/9/EC and Directive 2004/10/EC)
- 755 VICH GL9: Guideline on Good Clinical Practices (CVMP/VICH/595/1998)
- 756 VICH GL27: Guidance on the pre-approval information for registration of new veterinary medicinal
757 products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01)