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3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 **Guideline on the summary of product characteristics**
5 **(SPC) for veterinary medicinal products containing**
6 **antimicrobial substances**
7 **Draft**

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8 This guideline replaces the current CVMP guideline on the SPC for antimicrobial products
9 ([EMEA/CVMP/SAGAM/383441/2005](#)) and question 2 of the question & answer document
10 ([EMA/CVMP/414812/2011-Rev.2](#)).

11 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	Antimicrobial, summary product characteristics, SPC, veterinary medicinal products, responsible use, resistance, susceptibility testing, breakpoints
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¹ In view of the suspension of guideline work from 1 October 2018, as part of the Agency's business continuity plan, the consultation period has been extended and will finish at the end of August 2019 when the CVMP working party activities are expected to resume.



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41 **Executive summary**

42 This second revision of the guideline on the Summary of Product Characteristics (SPC) for antimicrobial
43 products provides updated guidance on the information to be included in the SPC of veterinary
44 medicinal products (VMPs) containing antimicrobial substances. It replaces the first revision of the
45 guideline on the SPC for antimicrobial products (EMA/CVMP/SAGAM/383441/2005), which came into
46 effect in May 2008. Since then there have been significant developments in principles of antimicrobial
47 therapy in regards to antimicrobial resistance and various regulatory initiatives have been undertaken
48 by CVMP (1-4), including publication of the CVMP's strategy on antimicrobials to 2020 (5). According to
49 these initiatives, recommendations from other CVMP reflection papers and referral procedures, and
50 based on experience gained from Marketing Authorisation procedures, further guidance is provided on
51 information to be included in the SPC in order to encourage optimal use and to minimise selection of
52 antimicrobial resistance. The second revision of the guideline should also serve to improve consistency
53 of the SPCs for antimicrobial products in the EU Member States.

54 **1. Introduction (background)**

55 The SPC is the key means of communication with the prescriber. It should contain the necessary
56 information making it possible to use the antimicrobial VMP effectively and safely while at the same
57 time minimising the risk of selection of antimicrobial resistance. Responsible use warnings and
58 recommendations for the specific VMPs should be included in the product information, and for this
59 purpose examples of relevant phrases for drafting an SPC are presented in this guideline. However,
60 warnings already covered by good veterinary practice in relation to responsible antimicrobial use
61 should not be part of the product information. An SPC drafted in accordance with this guideline should
62 provide essential background information on authorised products for people compiling national and
63 regional treatment guidelines (5).

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

66 **2. Scope**

67 This revised guideline provides instructions about specific information that should be included in the
68 SPC of VMPs containing antimicrobial substances. Defining a harmonised approach for the presentation
69 of the necessary information is considered useful for national and EU regulatory procedures.

70 This guideline applies to new marketing authorisation applications (where appropriate, depending on
71 the legal basis of the application as defined in Directive 2001/82/EC) and renewal applications. It also
72 applies to referrals and variation applications that require a reconsideration of the overall benefit risk
73 balance: for such procedures, it applies only to those parts of the SPC that fall within the direct scope
74 of the procedure.

75 **3. Legal basis**

76 The SPC should contain information in accordance with the requirements detailed in Article 14 of the
77 Directive 2001/82/EC (6) and other relevant EU and VICH guidelines. These include, but are not
78 limited to:

79 - the CVMP Guideline for the demonstration of efficacy for VMPs containing antimicrobial substances
80 (EMA/CVMP/627/2001-Rev.1) (1),

- 81 - the CVMP Guideline on the conduct of efficacy studies for intramammary products for use in cattle
82 (EMA/CVMP/EWP/344/1999-Rev.2) (7),
- 83 - the Guideline on the summary of product characteristics for pharmaceutical VMPs included in Volume
84 6C of the Rules Governing Medicinal Products in the European Union (8),
- 85 - VICH GL27 Guidance on pre-approval information for registration of new VMPs for food producing
86 animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL) (9),
- 87 and any guideline(s) derived from this.

88 **4. General considerations for the preparation of the SPC**

89 The following headings refer to the respective sections of the SPC. Sections where specific guidance
90 related to VMPs containing antimicrobial substances is not necessary do not appear in this guidance
91 document.

92 ***Section 4 Clinical particulars***

93 **Section 4.2 Indications for use, specifying the target species**

94 The intended use of the product should be clearly worded in the indication, i.e. the clinical
95 disease/signs to be treated. Indications for use must have defined causative bacterial target specie(s).
96 General indications without named target pathogens or indications with claims that are not related to a
97 clinical disease are not acceptable.

98 The target bacterial species shall be listed for each target animal species and for each indication for
99 use. Bacteria should be listed alphabetically in the following order: aerobic Gram-positive bacteria,
100 aerobic Gram-negative bacteria, anaerobic bacteria, and other micro-organisms.

101 Antimicrobial products should only be used when bacteria are susceptible to the antimicrobial
102 substance and, where feasible, in line with susceptibility testing according to guidance in section 4.5.
103 Hence, indications should not routinely need to use the wording: "<target bacterial species>
104 susceptible to <antimicrobial>".

105 The term "prevention" as a single and separate claim refers to the administration of an antimicrobial
106 VMP to an individual healthy animal to prevent bacterial infection if the risk for infection is very high
107 and the consequences are severe.

108 The term "treatment" refers to the treatment of an individual animal or a group of animals showing
109 clinical signs of an infectious bacterial disease.

110 The term "metaphylaxis" refers to group treatment of all clinically healthy (but presumably infected)
111 animals kept in close contact with animals showing clinical signs of a contagious disease. Metaphylaxis
112 is always combined with the treatment of the diseased individuals and consequently a metaphylaxis
113 claim will only be accepted in conjunction with a treatment claim. If metaphylaxis is part of the
114 indication, the following sentence must be included:

115 *"The presence of the disease in the group/flock must be established before the product is used."*

116 **Section 4.3. Contraindications**

117 Information may be added in this section where there is specific evidence of a serious risk to animal or
118 public health demonstrating that the product must not be used in a particular (subgroup of the target)

119 animal population. This may also relate to off-label use: for example, for 3rd and 4th generation
120 cephalosporins, the statement "Do not use in poultry" appears in section 4.3 following the assessment
121 of the risk to public health (4).

122 Selective effects of the antimicrobial on the normal gut microbiota (flora) leading to disruption of the
123 flora with serious consequences (e.g. use of colistin in foals and beta-lactams in rabbits and rodents)
124 should be stated. Alternatively, a warning could be included in section 4.5 where the consequences are
125 less serious but clinically relevant.

126 **Section 4.4 Special warnings for each target species**

127 The purpose of this section is to provide clear information on how to ensure the effective use of the
128 product in the target animals. Warning(s) may be needed if there is potential lack of efficacy of the
129 product in some situations.

130 Information on resistance should be included in cases where there may be an impact on the efficacy of
131 the product, e.g. when target bacteria show a multimodal distribution profile indicating a proportion of
132 isolates that may be clinically resistant and no clinical breakpoints are available, or when a significant
133 proportion of the bacterial target population is resistant in several geographical locations.

134 In case cross-resistance of a target pathogen(s) against member(s) of the same antimicrobial class or
135 related classes has been identified, the following information should be included:

136 *"Cross-resistance has been shown between <antimicrobial in the product> and <different
137 antimicrobial in the same (sub)class / related class> in <target bacteria>. Use of the <product
138 name/antimicrobial> should be carefully considered when antimicrobial susceptibility testing has
139 shown resistance to <antimicrobial(s)/classes of antimicrobials> because its effectiveness may
140 be reduced."*

141 Information regarding the absence of bacterial eradication (e.g. in *Mycoplasma* spp. infections) or
142 bacteriological cure (e.g. mastitis caused by *S. aureus*) may be included in this section.

143 For metaphylactic treatment, precise and thorough information should be provided about the
144 epidemiological circumstances under which the product has been shown to be effective (e.g. the
145 proportion of the group showing clinical signs at the start of treatment) and the extent of benefit
146 demonstrated. Where necessary, information should be included to give the product user realistic
147 expectations of the efficacy of the product and thereby reduce unnecessary antimicrobial use.

148 Information on clinical trials related to clinical efficacy may be included when related to the specific
149 circumstances of the trial (e.g. the substance has been used as a second line treatment and according
150 to Antimicrobial Advice Ad Hoc Expert Group (AMEG) classification, and should therefore be reserved
151 for use in certain situations only).

152 **Section 4.5 Special precautions for use**

153 ***i) Special precautions for use in animals***

154 **Recommendations for responsible use**

155 The purpose of this section is to provide clear information on how to ensure the safe use of the product
156 in the target animals. Warning(s) may be needed if there are potential safety risks associated with the
157 product in some situations.

158 One of the main requirements for the responsible use of antimicrobials is an accurate diagnosis before
159 treatment. Diagnosis should be confirmed preferably on isolation of the causative bacterial pathogen,
160 followed by antimicrobial susceptibility testing and use of accredited interpretive criteria (breakpoints)
161 aiming for a substantiated (calculated) therapy. This "gold standard" of good veterinary practice may
162 not always be feasible because of, for example, the acuteness/severity of the disease, inaccessibility of
163 bacteriological sampling, impossibility of bacterial isolation/cultivation, the lack of methods for
164 susceptibility testing or the lack of clinical breakpoints. Empirical therapy should then be based on local
165 epidemiological information concerning susceptibility of target bacteria.

166 For all antimicrobial products, the following should be included:

167 *"Use of the product should be based on identification and susceptibility testing of the target*
168 *pathogen(s). If this is not possible, therapy should be based on epidemiological information and*
169 *knowledge of susceptibility of the target bacteria at farm level, or at local/regional level."*

170 *"Use of the product should be in accordance with official, national and regional antimicrobial*
171 *policies."*

172 With regard to the antimicrobial risk to public health, antimicrobials are categorised depending on the
173 relative importance for their use in human medicine. These categories (AMEG, WHO) should be taken
174 into account to define whether a product should be reserved for use when response to other
175 antimicrobials is (expected to be) poor.

176 For certain substances in these categories, the CVMP has agreed to include specific precautionary
177 phrases in the SPCs (4, 10, 11), see Annex I.

178 Depending on the target animal species, the pharmaceutical form and the type of use, additional
179 recommendations on rational use may be necessary. Individual animal or group treatment will affect
180 the extent of the use of a product. In group treatment, the overall exposure of an antimicrobial, and
181 thus the potential to select for antimicrobial resistance, will be higher when compared to individual
182 treatment. If relevant, specific improvements to management and strategies for eradication can be
183 mentioned as further means to control particular infections where known to be effective. Inclusion of a
184 warning to discourage routine use as part of herd health programme may be necessary:

185 *"The <product name/antimicrobial> should not be used routinely as part of herd health*
186 *programmes."*

187 The following warning may be incorporated:

188 *"Use of the product deviating from the instructions given in the SPC may increase the prevalence*
189 *of bacteria resistant to <product name/antimicrobial> and may decrease the effectiveness of*
190 *treatment."*

191 A warning should be included where it is known that use of the antimicrobial may lead to co-selection
192 of resistance due to known associations between resistance mechanisms. (e.g. *Salmonella* Typhimurium
193 DT104 is frequently resistant to ampicillin, chloramphenicol/florfenicol, streptomycin sulphonamides
194 and tetracyclines).

195 For broad-spectrum antimicrobials e.g. extended-spectrum penicillins the following warning may be
196 included, if relevant:

197 *"Narrow spectrum antibacterial therapy with a lower risk of antimicrobial resistance selection*
198 *should be used for first line treatment where susceptibility testing suggests the likely efficacy of*
199 *this approach."*

200 For antimicrobial products used in dairy cows for which a withdrawal period for milk is established the
201 following warning should be included:

202 *The feeding of waste milk containing residues of <antimicrobial> to calves should be avoided up*
203 *to the end of the milk withdrawal period (except during the colostral phase), because it could*
204 *select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the*
205 *faecal shedding of these bacteria.*

206 **Section 4.8 Interaction with other medicinal products and other forms of** 207 **interaction**

208 Information should be given about clinically relevant pharmacological interactions where the
209 concurrent use of the substance with another one should be avoided. For example, polyvalent cations
210 are known to limit the absorption of some tetracyclines due to the formation of complexes, or
211 pleuromutilins have been shown to interact with ionophores with serious impacts on animal safety.
212 Cross-reference may be necessary to section 4.3.

213 Where evidence of clinically relevant synergism or antagonism between antimicrobials for specific
214 pathogens is available, this should be noted.

215 Information on cross-resistance should be indicated in section 4.4.

216 **Section 4.9 Amounts to be administered and administration route**

217 The recommended dose and duration of treatment included in this section of the SPC is based on the
218 efficacy and safety data of the product and should be as explicit as possible, and reflect the product
219 indications for the respective target species (production categories) and the route(s) of administration,
220 accordingly. Ranges in dose level should be avoided, unless there is clear guidance for the user as to
221 when to administer the product at the upper or lower limit of the range.

222 All deviations from approved and well justified dosing, recommended intervals, and treatment duration
223 of the antimicrobial product should be minimised. Further guidance such as recommendations on
224 discontinuation of treatment or re-evaluation of the diagnosis if no clinical response is seen in the
225 animal reflect good veterinary practice and should not be included in the SPC.

226 ***Section 5 Pharmacological properties***

227 The information submitted in this section should allow the prescriber to relate specific susceptibility
228 data (animal, farm, region) on the bacterial isolates to the mode of action and the kinetic profile of the
229 antimicrobial in order to allow a proper decision to be made on the use of the antimicrobial product,
230 and to achieve an optimal antibacterial effect and minimise the potential for selection of resistance in a
231 given situation.

232 **Section 5.1 Pharmacodynamic properties**

233 General properties of the antimicrobial should be described here, e.g. classification and mode of action,
234 if the substance is bactericidal or bacteriostatic, and if its effect is mainly time-dependent or
235 concentration-dependent.

236 The antibacterial spectrum relevant for the target animal species and approved indications should be
237 stated. The order of the listed micro-organisms should be the same as used in section 4.2. If possible,
238 MIC distribution data for the bacterial target pathogens should be provided, including information on
239 the number of analysed isolates, their origin (animal species, clinical condition, production type,

240 geographic area) and year when the isolates were collected. The epidemiological cut-off value (ECOFF)
241 should be provided, if feasible, to indicate the population without acquired resistance. The reference for
242 the ECOFF used should be given. If no ECOFF is available, MIC₅₀- and MIC₉₀-values should be
243 provided. Intrinsically resistant bacterial species should be mentioned if they are relevant in view of
244 the indicated use.

245 Clinical breakpoint(s) and MICs (µg/ml), if available, should be used to categorise isolates as
246 susceptible (S), intermediate (I) or resistant (R). The reference and the year of issue for the clinical
247 breakpoint(s) used should be given.

248 Information on the resistance mechanism(s) and the molecular genetics of acquired resistance in the
249 target pathogens should be included. The existence of any cross-resistance and co-resistance should
250 also be stated. Cross-reference may be necessary to section 4.4.

251 Antimicrobial susceptibility data for bacterial target species relevant to the clinical indications should be
252 updated based on any on-going EU surveillance programmes or other relevant information which might
253 influence the benefits and risks of the VMP.

254 **Section 5.2 Pharmacokinetic particulars**

255 Pharmacokinetic particulars of the product should be described in sufficient detail for clinical use.
256 Relevant pharmacokinetic parameters such as V_d, C_{max}, T_{max}, elimination half-life, clearance,
257 bioavailability and area under the concentration curve (AUC) should be mentioned for the
258 recommended route of administration and dosing regimen. The degree of protein binding of the
259 substance in the plasma should be given. Information about the concentrations of the free
260 antimicrobial at the site of infection should be provided, if available.

261 Where established, the most appropriate PK-PD index for the antimicrobial substance against each
262 pathogen may be indicated and also the magnitude of this index associated with clinical efficacy.

263 If different doses are proposed for different indications, concentrations in plasma should be mentioned
264 at least for the lowest and the highest dose.

265 Information on the excretion of the substance or active metabolites via the intestinal tract following
266 administration at the recommended dose should be given if available and if relevant to the approved
267 conditions of use.

268 **Section 6.5 Nature and composition of immediate packaging**

269 Full information about contents of the packaging, material in contact with the VMP, pack size(s) for the
270 particular pharmaceutical form and strength(s) is required.

271 For the prescribing veterinarian, it is especially important that appropriate pack size(s) is (are)
272 available for VMPs that may be administered by farmers/animal owners. These should be justified
273 taking into account the risks that might arise from inappropriate pack sizes, e.g. efficacy concerns if
274 pack size is too small or safety concerns if pack size is too large. In addition, of particular relevance to
275 antimicrobial products, the risks associated with leftovers should be considered, e.g. prolongation of
276 treatment duration or administration of the leftovers to other animals in the absence of veterinary
277 support.

278 It is fully acknowledged that establishing appropriate pack size can be very difficult. Several factors,
279 e.g. species, herd sizes and husbandry practices, affect what can be regarded as an appropriate pack
280 size and these factors can vary to a great extent between Member States. Some basic principles on
281 how to determine appropriate pack sizes are as follows:

282 • For products intended for the treatment of individual animals, one pack size should be available
283 and put on the market which is not larger than necessary to allow a full course of treatment of a
284 single animal of average size. However, where there is a large weight range for individuals in the
285 target population and/or there is more than one dosage regimen (different dose levels and/or
286 treatment durations), a suitable number of different pack sizes may have to be supplied.

287 • For products intended for the treatment of groups of animals, a pack size should be available that
288 does not contain more than the amount of product necessary to complete one treatment course in
289 a mean sized group of animals of average body weight with the lowest recommended dose and
290 shortest treatment duration. However, where the group size varies considerably within and/or
291 between Member States and/or a product is intended for use in more than one target species
292 and/or there are different indications with significantly different dosage regimens, different pack
293 sizes might be needed.

294 More information on the suitable pack sizes is in Annex II.

295 **Section 6.6 Special precautions for the disposal of unused veterinary** 296 **medicinal product or waste materials derived from the use of such products**

297 It is recommended that the following statement is included:

298 *“Any unused veterinary medicinal product or waste materials derived from such veterinary*
299 *medicinal product must be disposed of in accordance with local requirements.*”

300 **Definitions**

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

306 **Co-resistance:** The presence of resistance to more than one class of antimicrobial in the same
307 bacterial strain, as might occur when different resistance genes are found on the same plasmid.

308 **Co-selection of resistance:** The selection of multiple AMR genes when one of these is selected by the
309 presence of a relevant antimicrobial. An example of this is the integron, which may carry a gene
310 cassette(s) encoding AMR genes that is (are) under the control of a single promoter. As a result, these
311 genes are expressed in a coordinated manner, although the furthest downstream gene may not be as
312 efficiently expressed as the gene next to the promoter. These cassettes are commonly found in both
313 Gram-positive and Gram-negative bacteria. Since they can be part of a transposon they can become a
314 part of the bacterial chromosome or plasmid and can then be transmitted amongst different bacterial
315 strains.

316 **Cross-resistance:** A single resistance mechanism confers resistance to an entire class of
317 antimicrobials. An example is the aminoglycoside-modifying enzymes which may confer resistance to
318 several members of the aminoglycoside family. Cross resistance can occur across different classes of
319 agents - a result of either overlapping drug targets, as is the case with macrolides and lincosamides, or
320 a drug efflux pump with a broad range of activity (*i.e.* capable of exporting different classes of drugs).

321 **Metaphylaxis:** Group treatment of all clinically healthy (but presumably infected) animals kept in
322 close contact with animals showing clinical signs of a contagious disease. Metaphylaxis is always

323 combined with the treatment of the diseased individuals and consequently a metaphylaxis claim will
324 only be accepted in conjunction with a treatment claim.

325 **Prevention:** Administration of a VMP to individual healthy animals to prevent infection if the risk for
326 infection is very high and the consequences are severe.

327 **Treatment:** A treatment claim refers to the administration of a VMP after the onset of clinical signs of
328 disease and only clinically affected individuals are to be treated.

329 References

- 330 1. CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing
331 antimicrobial substances (EMA/CVMP/627/2001-Rev.1).
- 332 2. Question and answer on the CVMP guideline on the SPC for antimicrobial products
333 (EMA/CVMP/414812/2011-Rev.2).
- 334 3. CVMP/CHMP Answers to the requests for scientific advice on the impact on public health and
335 animal health of the use of antibiotics in animals (EMA/381884/2014).
- 336 4. Commission implementing decision of 13.1.2012 concerning, in the framework of Article 35 of
337 Directive 2001/82/EC of the European Parliament and of the Council, the marketing
338 authorisations for veterinary medicinal products which contain the active substances
339 "Cefquinome and Ceftiofur, [C\(2012\)182 final](#).
- 340 5. CVMP strategy on antimicrobials 2016-2020 (EMA/CVMP/209189/2015)
- 341 6. Directive 2001/82/EC of the European Parliament and of the Council, as amended.
342 Official Journal L 311, 28/11/2001 P. 0001 - 0066.
- 343 7. CVMP Guideline for the conduct of efficacy studies for intramammary products for use in cattle
344 (EMA/CVMP/EWP/344/1999-Rev.2)
- 345 8. Guideline on the summary of product characteristics for pharmaceutical veterinary medicinal
346 products included in Volume 6C of the Rules Governing Medicinal Products in the European
347 Union ([http://ec.europa.eu/health/files/eudralex/vol-6/c/spcpharmaceuticals_10-07-
348 2006_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-6/c/spcpharmaceuticals_10-07-2006_en.pdf)).
- 349 9. VICH GL27 Guidance on pre-approval information for registration of new veterinary medicinal
350 products for food producing animals with respect to antimicrobial resistance
351 (CVMP/VICH/644/01-FINAL)
- 352 10. CVMP Reflection paper on the use of fluoroquinolones in food producing animals - Precautions
353 for use in the SPC regarding prudent use guidance ([EMA/CVMP/416168/2006-FINAL](#)).
- 354 11. Commission implementing decision of 16.3.2015 concerning, in the framework of Article 35 of
355 Directive 2001/82/EC of the European Parliament and of the Council, the marketing
356 authorisations for all veterinary medicinal products containing "Colistin" to be administered
357 orally ([C\(2015\) 1916 final](#)).

358

359 **Annex I**
360 **Specific precautionary phrases to be included in section 4.5**

361 Specific precautionary phrases that have been agreed by CVMP to be included in section 4.5 as
362 recommendations for responsible use of fluoroquinolones, 3rd and 4th generation cephalosporins
363 administered systemically, and colistin administered orally in food producing animals:

364 **Fluoroquinolones (administered systemically)**

365 All fluoroquinolone products

366 "Official and local antimicrobial policies should be taken into account when the product is used."

367 "Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded
368 poorly, or are expected to respond poorly, to other classes of antimicrobials."

369 "Whenever possible, fluoroquinolones should only be used based on susceptibility testing."

370 "Use of the product deviating from the instructions given in the SPC may increase the prevalence of
371 bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other
372 quinolones due to the potential for cross resistance."

373 Quinolone products² (e.g. flumequine, oxolinic acid)

374 "Official and local antimicrobial policies should be taken into account when the product is used."

375 "Whenever possible, quinolones should only be used based on susceptibility testing"

376 "Use of the product deviating from the instructions given in the SPC may increase the prevalence of
377 bacteria resistant to the quinolones and may decrease the effectiveness of treatment with other
378 (fluoro-)quinolones due to the potential for cross resistance."

379 **3rd and 4th generation cephalosporins (administered systemically)**

380 Cefquinome, ceftiofur

381 Add, to all products:

382 "Product name (*to be completed nationally*)" selects for resistant strains such as bacteria carrying
383 extended-spectrum beta-lactamases (ESBL) and may constitute a risk to human health if these strains
384 disseminate to humans e.g. via food. For this reason, "*product name (to be completed nationally)*"
385 should be reserved for the treatment of clinical conditions which have responded poorly, or are
386 expected to respond poorly (refers to very acute cases when treatment must be initiated without
387 bacteriological diagnosis) to first line treatment. Official, national and regional antimicrobial policies
388 should be taken into account when the product is used. Increased use, including use of the product
389 deviating from the instructions given in the SPC, may increase the prevalence of such resistance.
390 Whenever possible, "*product name (to be completed nationally)*" should only be used based on
391 susceptibility testing.

392 "*Product name (to be completed nationally)*" is intended for treatment of individual animals. Do not
393 use for disease prevention or as a part of herd health programmes. Treatment of groups of animals
394 should be strictly restricted to ongoing disease outbreaks according to the approved conditions of use.

395 Add, where applicable, for products indicated for bovine metritis:

396 Do not use as prophylaxis in case of retained placenta.

² Not required for decoquinolate

397 **Polymyxins:**

398 Colistin (administered orally)

399 Add, to all products:

400 Do not use colistin as a substitute for good management practices.

401 Colistin is a last resort drug in human medicine for treatment of infections caused by certain multi-drug
402 resistant bacteria. In order to minimise any potential risk associated with widespread use of colistin, its
403 use should be limited to treatment or treatment and metaphylaxis of diseases, and should not be used
404 for prophylaxis.

405 Whenever possible, colistin should only be used based on susceptibility testing.

406 Use of the product deviating from the instructions given in the SPC may lead to treatment failures and
407 increase the prevalence of bacteria resistant to colistin.

408

409 **Annex II**
410 **Recommendations on the pack sizes suitable for**
411 **antimicrobial VMPs**

412 In general, any veterinary medicinal product (VMP) should be made available in a suitable pack size to
413 ensure the appropriate treatment of the intended target animal(s). For antimicrobial VMPs, adequate
414 pack size(s) should be chosen with particular care as an additional consideration to support their
415 prudent use.

416 A suitable number of different pack sizes may have to be supplied to allow dosing of individual animals
417 of different sizes, or different numbers of animals within a group. A reasonable balance has to be
418 identified between the need for different pack sizes to allow correct dosing without a significant amount
419 of leftovers, and the practical and economic difficulties that could be connected to the supply of many
420 different packages.

421 **Legal basis**

422 Specific reference to pack sizes in the veterinary legislation is sparse:

423 Annex I of Directive 2001/82/EC (as amended by 2009/9/EC; Art I, Part 2 A4 of Development
424 pharmaceuticals) states that "*An explanation shall be provided with regard to the choice of composition,*
425 *constituents, immediate packaging, possible further packaging, outer packaging if relevant, the*
426 *intended function of the excipients in the finished product and the method of manufacture of the*
427 *finished product. This explanation shall be supported by scientific data on development pharmaceuticals.*
428 *...."* Although the pack size is not specifically included in this paragraph of the Directive, the
429 information regarding the choice of packaging is not limited to the type of material, but would also
430 include considerations on e.g. the number of units in one pack or the fill volume of multidose or single
431 dose vials.

432 Furthermore, reference to pack sizes is made in the Variation Regulation, in regard to a change in the
433 pack size of the finished product (variation B.II.e.5). Conditions for such a change include that the new
434 pack size should be consistent with the approved posology and treatment duration, and that the
435 remaining presentation(s) must be adequate for the dosing instructions and treatment duration as
436 mentioned in the SPC.

437 Pursuant to Article 67 of Directive 2001/82/EC, as amended, "*Member States shall take all necessary*
438 *measures to ensure that, in the case of medicinal products supplied only on prescription, the quantity*
439 *prescribed and supplied shall be restricted to the minimum amount required for the treatment or*
440 *therapy concerned."* This fully applies to antibiotics, since they are supplied only on prescription within
441 the EU.

442 **Justification for the pack sizes**

443 Any pack size(s) for an application for marketing authorisation should be justified, taking into account
444 the risks that might arise from inadequate pack sizes (e.g. safety concerns in case of too large packs,
445 or efficacy concerns for too small pack sizes). It is particularly important that appropriate pack size(s)
446 is (are) available for VMPs that may be administered by the farmers/animal owners. Such products are
447 mainly formulations for oral administrations, but in some Member States injectable products can also
448 be administered by the animal owner under the responsibility of a veterinarian. If the pack size is too
449 large in regard to the animal(s) to be treated and/or the recommended treatment period, leftovers
450 may be misused, e.g. by prolonging the treatment period or by administration to other animals without
451 veterinary support.

452 It is fully acknowledged that establishing the appropriate pack size is very difficult. Several factors e.g.
453 species, herd sizes and husbandry practices affect what can be regarded as an appropriate pack size,
454 and these factors can vary to a great extent both within and among Member States. Notwithstanding
455 these difficulties, some basic principles on how to determine an appropriate pack size are given in this
456 document. The principles for determining a suitable pack size differs substantially between the
457 situation when only one animal is to be treated, or when group treatment is applied. For this reason,
458 advice is given separately for packages intended for individual treatment and for group treatment.

459 **Individual treatment**

460 For products intended for individual treatment, the dosage, treatment duration, and the average
461 bodyweight of the animal species for which it is indicated will define the minimum amount required for
462 one treatment course. As a basic requirement, one package should be available which is not larger
463 than necessary to allow the full course of the treatment of one single animal of average size. When the
464 total amount needed to complete a full course of treatment varies considerably due to e.g. different
465 sizes of the animals, dosages or duration of administration, different pack sizes should be made
466 available.

467 Any additional pack size which is larger than necessary to treat one single animal would have to be
468 carefully justified. In case of multi-dose packages, e.g. vials for injectables intended to be used by a
469 veterinarian to treat several animals, the amount of VMP per vial would have to be justified taking into
470 account of the disease and species to be treated. In some EU countries, the veterinarian may
471 provide vials to the animal owner to complete a treatment episode. The size of the multi-dose vial
472 would have to be adapted taking into account of such use to ensure that it would not result in
473 substantial amounts of left-overs.

474 **Group treatment**

475 The definition of appropriate pack size(s) for products intended for group treatment, would have to
476 include an estimation of the average number and weight of the animals that will be concomitantly
477 treated for the particular disease, within the intended area(s)/country(ies). Since these parameters
478 vary considerably among Member States and between diseases, acceptable figures cannot be given in
479 this document.

480 As a general rule, and in account of what is mentioned above one pack size should be made available
481 that contains not more than the amount necessary to complete one treatment course in a mean size
482 group of animals of an average body weight with the lowest recommended dose and shortest
483 treatment duration. If the size of a group of the target population varies considerably within or
484 between Member States, several pack sizes might need to be made available.

485 When a product is intended for use in more than one target species or different indications with
486 significantly different recommended dosages and duration of administration, different pack sizes should
487 be made available. Any pack size which differs from the one ensuring the minimum amount necessary
488 - established according to the principles above - should be carefully justified by the applicant.

489 **Individual and group treatment**

490 If a product is intended for both group and individual treatment, ideally two pack sizes should be made
491 available. One should allow the full course of one treatment of one single animal, with the smallest
492 recommended dose and duration of treatment. The other pack size should cover the full course of one
493 treatment of a group of animals according to the principles outlined under "Group treatment". Any

494 pack size which differs from the ones ensuring the minimum amount required - established according
495 to the principles above - should be carefully justified by the applicant.

496 **Overall conclusions**

497 A minimum pack size that would allow the completion of one treatment course in an individual animal
498 or in a mean size group of the target animals, of an average body weight with the lowest
499 recommended dose and shortest treatment duration should always be supplied.

500 A justification for the pack sizes presented in connection to an application for marketing authorisation
501 should always be provided, in particular any pack size(s) which differs from the one ensuring the
502 minimum amount necessary.

503 Livestock, herd sizes and diseases can vary across Member States, and Member States might therefore
504 decide to apply individual measures in regard to the distribution/supply of certain pack size(s) in their
505 country (subject to national legislation/implementation of Art. 67 of Directive 2001/82/EC).