



1 12 February 2015
2 EMA/CVMP/AWP/706442/2013
3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 **Guideline on the assessment of the risk to public health**
5 **from antimicrobial resistance due to the use of an**
6 **antimicrobial veterinary medicinal product in food-**
7 **producing animals**
8 **Draft**

Draft agreed by Antimicrobials Working Party	21 January 2015
Adopted by CVMP for release for consultation	12 February 2015
Start of public consultation	4 March 2015
End of consultation (deadline for comments)	31 August 2015

9
10

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

11
12



13 Guideline on the assessment of the risk to public health
14 from antimicrobial resistance due to the use of an
15 antimicrobial veterinary medicinal product in food-
16 producing animals

17 **Table of contents**

18	Executive summary	3
19	1. Introduction (background)	3
20	2. Scope.....	3
21	3. Legal basis	4
22	4. When does this guidance apply?.....	4
23	5. Methodology for the risk assessment	5
24	6. Data sources and quality	9
25	7. Data requirements.....	9
26	7.1. Hazard identification	9
27	7.2. Release assessment.....	10
28	7.3. Exposure assessment	13
29	7.4. Consequence assessment	14
30	8. Overall qualitative risk estimation.....	16
31	Definitions.....	16
32	References	18
33		

34 **Executive summary**

35 This guideline provides advice in regards to applications for Marketing Authorisations for antimicrobial
36 veterinary medicinal products (VMPs) on the data required and the methodology to be used for
37 performing an assessment of the risk to public health from antimicrobial resistance (AMR) due to use
38 of the product. The scope of the guidance extends to VMPs intended for food producing species and to
39 the transmission of AMR by the foodborne route or through direct contact with treated animals.

40 The risk assessment methodology is adapted from that described by the World Organisation for Animal
41 Health (OIE). Other relevant methodology such that of Codex Alimentarius was also taken into account
42 for the preparation of this guidance (see chapter 5.). The steps required take into account: the
43 identification of resistant bacteria or resistance determinants that could be associated with human
44 illness and are selected by the use of the antimicrobial VMP in animals; the probability of exposure of
45 zoonotic and commensal bacteria in the target animal species based on the conditions of use of the
46 VMP under consideration; the probability of subsequent human exposure to AMR, and the resulting
47 consequences to human health. Guidance is given on data quality and possible data sources for each
48 step of the risk assessment process. It is recognised that there will be data gaps and therefore it is
49 recommended that a qualitative approach is taken to give a final estimation of the overall risk to public
50 health due to AMR.

51 **1. Introduction (background)**

52 The CVMP Strategy on Antimicrobials 2011-2015¹ advises that CVMP will consider available data on
53 antimicrobial resistance (AMR) and give AMR-related risks adequate weight in the benefit-risk
54 assessment when deciding to authorise, or restrict use of, an antimicrobial veterinary medicinal
55 product. In regards to the risk to public health, food has always been regarded as an important route
56 through which human beings may be exposed to antimicrobial-resistant bacteria, and there is now
57 increasing concern in regards to the risk of exposure through direct contact with livestock for certain
58 organisms. Although the VICH GL 27² already provides guidance on data requirements for registration
59 of new veterinary medicinal products for food producing animals with respect to AMR, not all aspects of
60 the risk assessment are addressed and there are no recommendations on how the final risk estimation
61 should be concluded. Increasing concern has been raised from many parties in regards to the impact
62 on public health of the use of antimicrobials in animals. Therefore, this guidance on the risk
63 assessment part of the risk analysis process for antimicrobial veterinary medicinal products is aimed to
64 provide a systematic approach to the evaluation of the associated scientific data and to improve the
65 transparency and consistency of the regulatory decision-making process.

66 **2. Scope**

67 The purpose of this guideline is to provide guidance on the data required and the methodology to be
68 applied to the assessment of the risk to public health from AMR in relation to Marketing Authorisation
69 applications for antimicrobial veterinary medicinal products for use in food producing species. The
70 consequences of AMR that may be considered include loss of treatment options, human illness
71 (morbidity), hospitalisation and death (mortality).

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109137.pdf

² VICH GL 27: Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance. <http://www.vichsec.org/en/topics.htm#8>

72 The risk question to be addressed is:

73 *What is the risk to public health from antimicrobial-resistant bacteria resulting from the intended use*
74 *of the proposed veterinary medicinal product?*

75 The scope of this guidance extends to:

- 76 • Veterinary Medicinal Products (VMPs) intended to treat food producing species, and
77 • Antimicrobial VMPs that potentially select resistant bacteria and that may be transmitted through
78 foodstuff of animal origin or by direct contact with the target species and have an impact on
79 human health.

80 Direct contact relates to exposure through handling animals or animal products and may therefore be
81 relevant for those such as farm workers, animal owners, veterinarians, abattoir workers, those
82 handling food of animal origin and people (including children) who may visit farms.

83 Although there are many other potential routes of human exposure to antimicrobial-resistant bacteria
84 (e.g. via general environmental contamination) it is currently difficult to attribute the resistance to use
85 of VMPs and these routes are not within scope of this guidance. VMPs for companion animals, including
86 horses not intended for human consumption, are also excluded from the scope of this guidance. The
87 EMA/CVMP/AWP has recently published a reflection paper on the risk of antimicrobial resistance
88 transfer from companion animals (EMA/CVMP/AWP/401740/2013)³.

89 The steps of risk management and risk communication that are essential for a complete risk analysis
90 are not discussed in this guideline. It is, however, acknowledged that the risk assessment process may
91 help to identify appropriate risk management steps and the data provided for the risk assessment
92 should be tailored to the veterinary medicinal product in question and the specific conditions of its use
93 where relevant. "Off label" use, including misuse, does not have to be considered within the risk
94 assessment.

95 **3. Legal basis**

96 This guideline should be read in conjunction with the introduction and general principles and
97 requirements for safety tests laid out in Annex I to the Directive 2001/82 as amended, which requires
98 data to be provided on the potential for emergence of antimicrobial-resistant bacteria of relevance for
99 human health.

100 **4. When does this guidance apply?**

101 The specified data and risk assessment should be provided in support of:

- 102 • Any Marketing Authorisation application for an antimicrobial substance not previously authorised
103 for use in a veterinary medicinal product for food producing species in the EU.
- 104 • Any application for a combination of antimicrobial substances not previously authorised for use in a
105 veterinary medicinal product for use in food producing species in the EU.
- 106 • Any application relating to an antimicrobial substance previously authorised for use in a food
107 producing species that could lead to an increase in volume of use or an increased risk to public
108 health, e.g.:

³ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500181642.pdf

- 109 — A change to the dosage form or pattern of use or exposure e.g. a change from
 - 110 individual animal use to group medication; a change in the formulation from injectable
 - 111 to in-feed/in-water medication.
 - 112 — Extension to a new major food-producing species.
 - 113 — Addition of another major group within the same food-producing species (e.g. beef
 - 114 cattle to dairy cattle).
 - 115 — Addition of new major therapeutic indications.
 - 116 — Any change to the dosing regimen.
- 117 A separate risk assessment should be provided for each formulation/ animal species/ indication/ dosing
- 118 regimen, although parts of the assessment are common to more than one scenario.
- 119 The guidance does not apply for generic applications made under Article 13.2 of the Directive.
- 120 For other cases, such as Marketing Authorisation applications for minor species or minor indications, a
- 121 risk assessment should be provided unless a justification can be given that this will not present a new
- 122 hazard or significantly increase the exposure to AMR.

123 5. Methodology for the risk assessment

124 The risk assessment methodology has been adapted from that that described by the OIE (Antimicrobial

125 resistance: risk analysis methodology for the potential impact on public health of antimicrobial

126 resistant bacteria of animal origin; Vose et al, 2001⁴; OIE Terrestrial Animal Health Code, chapter

127 6.10). In addition, note has been taken of the methodology proposed by Codex (Guidelines for risk

128 analysis of foodborne antimicrobial resistance, CAC/GL 77-2011⁵) and the requirements in place in

129 other jurisdictions (FDA⁶, Health Canada⁷, APVMA⁸). The OIE methodology is used as the basis for this

130 CVMP guidance to facilitate alignment with models used in other regulatory jurisdictions and due to the

131 particular applicability of the “release assessment” step to the risk analysis for VMPs. The methodology

132 takes into account: knowledge of the mechanisms of resistance to the antimicrobial under

133 consideration; the probability of exposure of zoonotic and commensal bacteria in the target species

134 based on the conditions of use of the veterinary medicinal product under consideration; the probability

135 of subsequent human exposure to AMR via food or direct animal contact and also, as the assessment

136 relates to the risk to public health, the importance of the antimicrobial substance to human medicine

137 and consequences to human health. As the risk assessment is for a specific antimicrobial VMP, more

138 emphasis is placed on the impact of the conditions of use relevant to the product, and less emphasis

139 on aspects that relate to risk factors that are not product-related e.g. impact of methods of food

140 processing on bacterial load in foods.

⁴ Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin. Vose D, Acar J, Anthony F, Franklin A, Gupta R, Nicholls T, Tamura Y, Thompson S, Threlfall EJ, van Vuuren M, White G, Wegener HC, Costarrica ML. Rev.sci.tech.Off.int.Epiz., 2001, 20(3),811-827.

⁵ <http://www.codexalimentarius.org/search-results/?cx=018170620143701104933%3Ai-zresgmxec&cof=FORID%3A11&q=antimicrobial&siteurl=http%3A%2F%2Fwww.codexalimentarius.org%2F&sa.x=19&sa.y=9>

⁶ US Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine, October 23, 2003. Guidance for Industry #152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern.

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123614.htm>

⁷ Health Canada, Veterinary Drugs Directorate Guidance for Industry – 2005. Guidance document for microbiological safety studies requirements for preparation of veterinary new drug submissions. Health Canada: http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr-ram_rep-rap_06_05-eng.php

⁸ Australian Pesticides and Veterinary Medicines Authority. Veterinary Manual of Requirements and Guidelines, Part 10 – Special Data: Antibiotic Resistance. http://www.apvma.gov.au/morag_vet/vol_3/part_10_special.php

141 The following steps in the risk assessment structure should be followed:

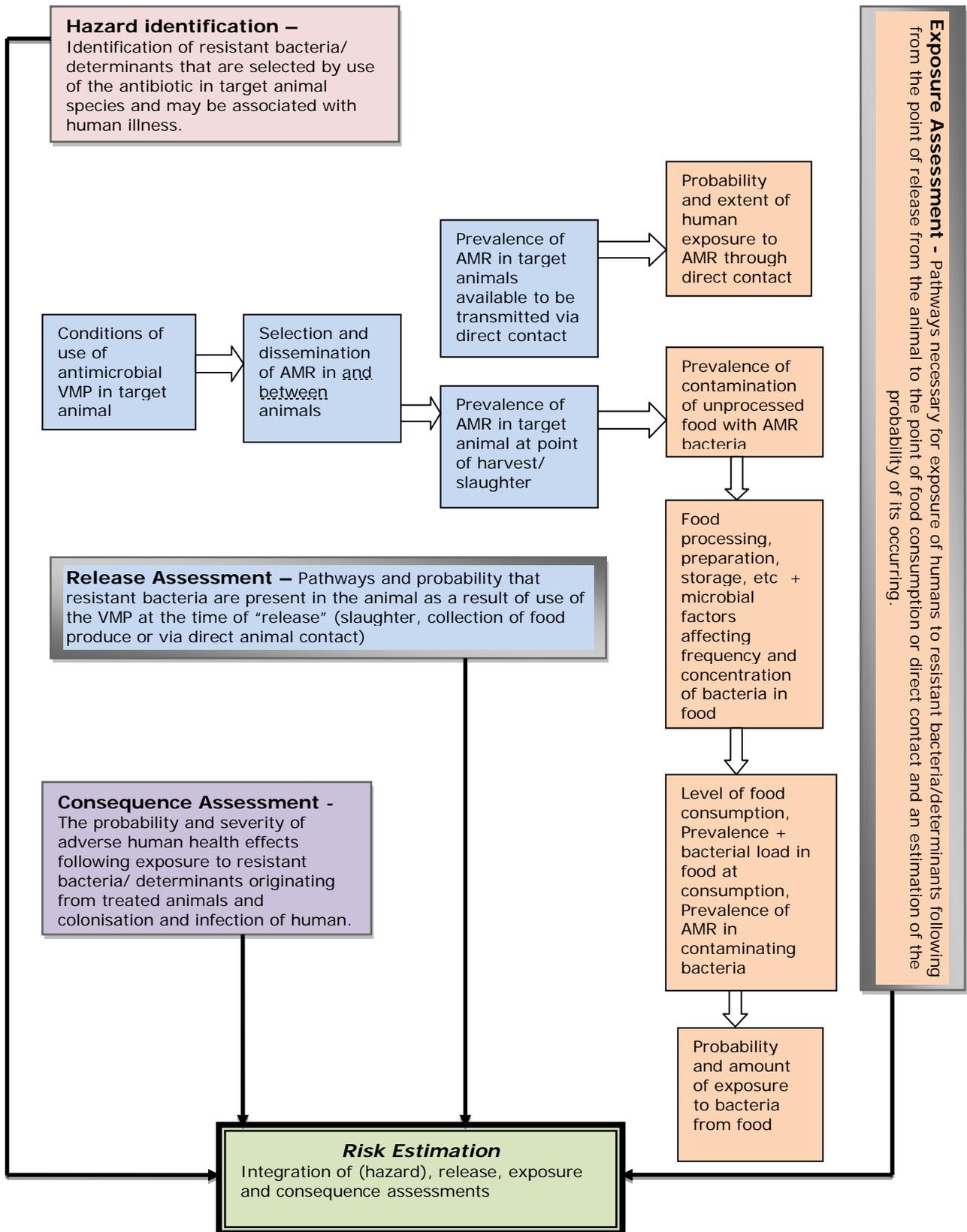
- 142 • **Hazard identification:** the identification of antimicrobial-resistant bacteria or resistance
143 determinants therein that could be associated with human illness and are selected due to the use
144 of the concerned antimicrobial substance in the target animal species. Resistance may develop
145 both in bacteria that are zoonotic and/or in commensal bacteria in animals that could pass
146 resistance determinants to other bacteria that are pathogenic in humans.
- 147 • **Release Assessment:** the biological pathways necessary for use of the specific antimicrobial
148 veterinary medicinal product in the target species and to bring about development of resistant
149 bacteria in the animal up to the time of “release” at slaughter, collection of food produce or
150 through direct contact with a handler, and an estimation of the probability of that complete process
151 happening.
- 152 • **Exposure Assessment:** the biological pathways necessary for exposure (via food or direct
153 contact) of humans to the identified hazard(s) (resistant bacteria/determinants) following from the
154 point of release from the target species to the point of food consumption or direct contact, and an
155 estimation of the amount of exposure and probability of its occurring.
- 156 • The division of the risk assessment into “release” and “exposure” components effectively separates
157 animal and animal treatment factors that are associated with use of the specific VMP (release) from
158 food-chain and human factors (exposure).
- 159 • **Consequence Assessment:** The potential consequences (adverse health effects) of exposure of
160 humans to the hazard and the severity and probability of the consequences occurring. The
161 consequence assessment for resistant bacteria may be informed by that for non-resistant
162 organisms; however, it relates to consequences over and above those caused by a antimicrobial-
163 sensitive strain of a pathogen, and unless the resistance also results in increased transmission or
164 virulence, only to circumstances where antimicrobial treatment would be required. [In accordance
165 with Codex, this step is also known as “Hazard Characterisation”].
- 166 • **Risk estimation:** The integration of the key findings from the release, exposure and consequence
167 assessments to produce an overall measure of the risk associated with the hazard identified at the
168 outset. The risk estimation therefore takes into account the entire risk pathway from the hazard(s)
169 identified to the unwanted outcome.

170 It is recognised that there are likely to be substantial data gaps that preclude a quantitative approach
171 to this risk assessment. Likewise, given the current level of knowledge and data available, semi-
172 quantitative categorisation of the factors on the risk pathway and subsequently the steps in the risk
173 assessment might be arbitrary. Therefore use of a risk matrix based on the categorisation of the
174 individual steps is not proposed as they cannot be logically combined to determine an overall effect.
175 Consequently, this guidance proposes that a qualitative approach is taken, although, where
176 quantitative data are available applicants are encouraged to refine the approach. A structured and
177 transparent approach should still be taken to the assessment. The applicant should comment on any
178 assumptions that have been made, especially in relation to data gaps or poor understanding of risk
179 pathways. The uncertainty and variability associated with each factor/parameter and the influence this
180 may have on the reliability of the overall risk assessment should be evaluated. Within this context, the
181 risk assessor should still aim to provide a clear summary of the available data and conclusion at the
182 end of each step of the assessment.

183 The risk assessment should take into account the proposed conditions and anticipated extent of use of
184 the veterinary medicinal product (e.g. target species, indication, route of administration, treatment

185 incidence, see below 7.2) and is therefore specific to those circumstances. An acceptable level of risk is
186 that which when weighed against the proposed benefits of use of the veterinary medicinal product in
187 the target species, will not significantly compromise therapeutic use of antibiotics in humans or human
188 health. Risk management measures to minimise the risk to public health from use of the VMP may also
189 be taken into account. The acceptability of the risk level has to be weighed in the context of the overall
190 benefit-risk as determined from the complete dossier for the product. This aspect is not addressed
191 further here as this guidance document only addresses the risk assessment process. Further guidance
192 on the evaluation of the benefit-risk for VMPs is given in the document: recommendation on the
193 evaluation of the benefit-risk balance of veterinary medicinal products (EMA/CVMP/248499/2007).

194 **Figure 1:** Possible pathways and components of antimicrobial risk assessment for a veterinary
 195 medicinal product for use in food producing species.



196
 197

198 6. Data sources and quality

199 Possible sources of information include, for example, data included in other sections of the dossier
200 (e.g. pharmacodynamics, residues), information from national and EU databases (EMA, EFSA, ECDC),
201 investigations of outbreaks or sporadic cases of infections associated with AMR organisms, and
202 scientific studies investigating the potential for antimicrobial substances to select for antimicrobial-
203 resistant organisms and the transfer of genetic determinants. Acceptable data will include sponsor-
204 generated studies, official reports and peer-reviewed literature references. Sponsor generated studies
205 should (ideally) be conducted in compliance with GLP and/or GCP, as applicable. For MIC studies, data
206 for key organisms should be consistent with the requirements in VICH GL 27 and where originating
207 from surveillance programmes, these should be relevant to the EU for the last 5 years. For new
208 antimicrobial substances that have not previously been used within the EU, then information from third
209 countries may be of value if available. In addition, if substance-specific data are not available, then
210 reference may be made to related molecules within the same antimicrobial class, in which case a
211 justification of the relevance of the reference should be provided.

212 When data are not available in public literature or from the sponsor's own studies, then expert opinion
213 may be used. In this case, it is better for the applicant to solicit the views of more than one expert.

214 7. Data requirements

215 7.1. Hazard identification

216 This step addresses the identification of antimicrobial-resistant bacteria or resistance determinants that
217 could result in human illness and may be selected due to the use of the concerned antimicrobial
218 substance in the target animal species. Resistance may develop both in bacteria that are zoonotic
219 and/or in commensal bacteria in animals that could pass mobile-mediated resistance determinants to
220 other bacteria that are pathogenic in humans. For the purpose of this risk assessment, only bacteria
221 that are foodborne or may be transferred by direct contact with animals need to be considered.

222 **Table 1:** Hazard identification, data requirements and guidance.

Data required	Detail	Further guidance on resources
Substance-specific information.	Antimicrobial class.	See VICH GL 27, section 1.1
	Mechanism of action.	See VICH GL 27, section 1.2
	Spectrum of activity.	See VICH GL 27, section 1.3
Taking into account the target animal species to be treated, the applicant should identify and justify the bacterial species for which resistance to the antimicrobial of concern has potential human health consequences.	This includes: <ul style="list-style-type: none">• Foodborne pathogens (e.g. <i>Campylobacter</i>, <i>Salmonella</i>);• Bacteria that could be transmitted by direct contact (e.g. <i>Staphylococcus aureus</i>);• Indicator/commensal bacteria that may carry	See VICH GL27, section 1.3. In addition consider bacteria that may be transmitted by direct contact.

Data required	Detail	Further guidance on resources
	mobile resistance determinants that could be passed to human pathogenic bacteria (e.g. <i>Escherichia coli</i> , <i>Enterococcus</i> spp).	
Known resistance determinants or mechanisms associated with the antimicrobial in animal and human bacteria.	E.g. antimicrobial inactivation, alteration of target, efflux pumps. Location of resistance determinants, e.g. chromosomal, plasmid, transposons.	See VICH GL 27, section 1.4 Cross-reference can be made, as appropriate to the information supplied in accordance with the revised CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances.
Occurrence of cross-resistance and co-resistance.	This relates to antimicrobials approved for use in both human and/or veterinary medicine whose efficacy could be compromised. Both a phenotypic and genotypic description should be provided.	See VICH GL 27, sections 1.6 and 1.7 Cross-reference can be made, as appropriate to the information supplied in accordance with the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (currently under revision).
Susceptibility data (MIC distribution /MBC) for the bacteria of human health concern.	MIC values should be determined with validated methods, where possible. Clinical and microbiological breakpoints (ECOFFs) should be considered in the assessment.	See VICH GL 27, section 1.3

223 The applicant should provide a discussion that leads to an overall conclusion on the opportunity for
224 development of antimicrobial-resistant bacteria /determinants that could result in human illness, and
225 may be selected due to the use of the concerned antimicrobial substance in the target animal species.

226 **7.2. Release assessment**

227 This step addresses the biological pathways necessary for use of the specific antimicrobial veterinary
228 medicinal product in the target species and to bring about selection of resistant bacteria in the animal
229 up to the time of "release" at slaughter, harvest of food produce from the animal or direct contact with
230 a handler, and an estimation of the probability of that complete process happening.

231 **Table 2:** Release assessment, data requirements and guidance.

Data required	Detail	Further guidance on resources and interpretation of data
Product description	Formulation	
Conditions of use	Target species and production type (e.g. beef cattle); husbandry practices; disease indication and its prevalence; estimate of the number and age (body weight) of animals likely to be exposed in a given time frame; potential for dissemination of AMR between animals and premises.	Eurostat ⁹ , ESVAC ¹⁰ data on PCU ¹¹ . Higher risk would be associated e.g. with common diseases requiring regular treatment, major species; husbandry requiring high level of human contact with the target group. Lower risk would be associated with minor species, rare diseases.
Resistance selection pressure	Envisaged extent of use of the product: dose regimen and justification for duration of use; route of administration (individual/mass, local/systemic, parenteral/oral) Selection pressure from AMs that may induce co-/cross-resistance.	ESVAC sales data. Higher risk would be associated with herd/flock treatments, especially those administered orally via food or drinking water. Lower risk would be associated with individual animal treatments, and with products which are administered locally so that gastrointestinal-tract exposure is limited. Longer duration of treatment effect could be associated with higher risk of AMR selection.
PK/PD of the antimicrobial	ADME ¹² in the target animal species. PD: concentration- or time-dependent effects, PAE ¹³ , sub-MIC ¹⁴ effects etc. PK/PD ¹⁵ in respect of bacterial species identified as potential hazards to human health.	Some of this information may be obtained from Part 4 of the dossier, in accordance with the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (currently under revision).

⁹ Eurostat is the statistical office of the European Union.
<http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/>

¹⁰ The European Surveillance of Antimicrobial Consumption.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

¹¹ PCU: Population Correction Unit, as used by ESVAC. See
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp

¹² ADME: absorption, distribution, metabolism, excretion.

¹³ PAE: post antibiotic effect

¹⁴ MIC: minimal inhibitory concentration

¹⁵ PK/PD: pharmacokinetics/pharmacodynamics

Data required	Detail	Further guidance on resources and interpretation of data
Occurrence and rate of transfer of resistance determinants	<p>Studies may be included to demonstrate both <i>in vitro</i> or <i>in vivo</i> rate and extent of resistance development. This may include studies conducted in laboratory animals or the target species, and <i>in vitro</i> mutation frequency studies.</p> <p>Can resistance determinants be transferred horizontally between bacteria and to bacteria of different species (transformation, transduction, conjugation) and at what rate? Do findings from <i>in vitro</i> conditions reflect field situation?</p>	<p>See VICH GL 27, sections 1.5 and 2.1</p> <p>See information in response to Q.2 of the Commission's request for scientific advice on the impact on public and animal health of the use of antibiotics in animals (EMA/381884/2014, Table 3)¹⁶.</p>
Estimation of the concentration of the antimicrobial agent in the intestinal lumen of the target animal under proposed conditions of use and expected effects on colon microbiota.	Antimicrobial activity may be due to parent antimicrobial or metabolites. An indication should be given of the expected effects on resistance selection in the intestinal microbiota and on the possible duration of shedding of resistant organisms.	<p>See VICH GL 27, section 2.2.</p> <p>It may be possible to extrapolate from data contained in Part 3 of the dossier (microbiological properties of residues), where specific data for the target species are not available.</p> <p>Higher risk would be associated with antimicrobial concentrations ranging within the selective window for relevant organisms of the microbiome.</p>
Prevalence of carriage of zoonotic bacteria and commensals in target animal population and baseline prevalence of resistance in those bacteria.	<p>Epidemiological data on the existing prevalence of resistance to the antimicrobial in question and related antimicrobials in zoonotic bacteria and commensals identified as potential hazards in the target animal.</p> <p>In relation to direct contact, literature studies may be available on skin carriage of relevant bacteria in the target species and prevalence in the immediate farm</p>	<p>E.g. The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks (EFSA/ECDC).¹⁷</p> <p>The European Union Summary Report on Antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union (EFSA/ECDC)¹⁸ Other sources may also be used, e.g. CEESA.¹⁹</p>

¹⁶ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf

¹⁷ <http://www.efsa.europa.eu/en/topics/topic/monitoringandanalysisoffood-borne-diseases.htm#wtrl=01>

¹⁸ <http://www.efsa.europa.eu/en/topics/topic/amr.htm>

¹⁹ The European Animal Health Study Centre (CEESA): European Antimicrobial Susceptibility Surveillance in Animals Programme (EASSA).

Data required	Detail	Further guidance on resources and interpretation of data
	environment.	
Other relevant information	Studies to investigate rate of resistance selection in foodborne bacteria following use of the product under proposed conditions of use and rate of decline after cessation of therapy, in relation to time of slaughter/harvest.	Influence of withdrawal period or period between treatment and slaughter could be considered in the assessment.

232 The applicant should provide a discussion that leads to the overall conclusion on the probability that
 233 antimicrobial-resistant bacteria/determinants will be selected for and “released” as a result of the
 234 proposed use of the product in animals.

235 **7.3. Exposure assessment**

236 This step addresses biological pathways necessary for exposure (via food or direct contact) of humans
 237 to the hazard(s) (resistant bacteria/determinants) following from the point of release from the target
 238 species to the point of food consumption or direct contact, and an estimation of the amount of
 239 exposure and probability of its occurring.

240 The division of the risk assessment into “release” and “exposure” components effectively separates
 241 animal and animal treatment factors that are associated with use of the specific VMP (release) from
 242 food-chain and human factors (exposure). It is acknowledged that certain factors such as the way that
 243 food of animal origin is processed, transported, stored and cooked have a strong influence on microbial
 244 load in specific food products at the point of consumption. These factors are assumed to be
 245 independent of the conditions of use of a specific antimicrobial VMP. In order to simplify the approach,
 246 the factors a) to d) below may be used as the minimum data set to summarise the final estimate of
 247 foodborne exposure. Where point of consumption data are unavailable, data from an earlier stage of
 248 the risk pathway (e.g. at point of sale) might be provided as an alternative if justified.

249 **Table 3:** Exposure assessment, data requirements and guidance.

Data required	Detail	Further guidance on resources
a) Human consumption patterns for food produce from target species in the EU	This refers to major produce classes associated with the target animal, e.g. meat (beef, pork, chicken, turkey, etc); dairy produce; fish; eggs	EFSA EU Comprehensive Food Consumption Database ²⁰ /Eurostat
b) Prevalence of food contamination at point of consumption with relevant bacteria		EFSA/ECDC Zoonosis reports

²⁰ <http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm>

Data required	Detail	Further guidance on resources
c) Microbial load of food at point of consumption		
d) Prevalence of resistance to antimicrobial in those bacteria		The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food
e) <u>Data from source attribution studies</u>	Please refer to Scientific Opinion of the Panel on Biological Hazards on a request from EFSA ON Overview of methods for source attribution for human illness from foodborne microbiological hazards. <i>The EFSA Journal</i> (2008) 764,1-43 ²¹	
f) Data to characterise probability of human exposure through direct contact, e.g. number of people exposed to the animal during rearing, carcass at slaughter and processing, farm visits		A distinction between professional contact (occupational hazard reports) and occasional contact (e.g. children on farm visits) might be indicated

250 The applicant should provide a discussion that leads to the overall conclusion on the amount of
251 exposure of humans to antimicrobial-resistant organisms/determinants via food at the point of
252 consumption or through direct contact, and the probability of its occurring.

253 **7.4. Consequence assessment**

254 This step addresses the potential consequences (adverse health effects) of exposure of humans to the
255 hazard(s) and the severity and probability of the consequences occurring.

256 The consequence assessment for resistant bacteria may be informed by that for non-resistant
257 organisms; however, it relates to consequences over and above those caused by a sensitive strain of a
258 pathogen, and unless the resistance also results in increased virulence, only to circumstances where
259 antimicrobial treatment would be required.

260 It is acknowledged that there may be a high level of uncertainty in the estimate of the proportion of
261 infections due to resistant organisms in humans that can be attributed to animal sources, especially
262 where the resistance originates from commensals.

²¹ <http://www.efsa.europa.eu/en/efsajournal/pub/764.htm>

263 **Table 4:** Consequence assessment, data requirements and guidance.

Data required	Detail	Further guidance on resources
a) Relative importance of the antimicrobial to human medicine	<p>Spectrum of activity and indications for use in humans.</p> <p>Availability of alternative antimicrobial treatments.</p> <p>Extent of use in human medicine.</p>	<p>See information in response to Q.2 of the Commission’s request for scientific advice on the impact on public and animal health of the use of antibiotics in animals (Table 2).</p> <p>ESAC database²².</p>
b) Dose-response relationships (where available)	<p>A description of the relationship between the frequency and magnitude of exposure of humans to the resistant organisms and the severity and frequency of the impact; including an estimate of the critical threshold of exposure required to cause infection in susceptible humans.</p>	
c) Consequences of AMR in human infections	<p>Number of cases of human infection reported (and estimate of unreported cases) per annum.</p> <p>Number/proportion of cases attributed to animal food produce/animal contact.</p> <p>Severity of disease: deaths, long term impacts, number of days illness, hospitalisation (length of stay, additional treatment).</p> <p>Prevalence of antimicrobial resistance in human isolates and attribution to animal source (where possible).</p> <p>Any increase in transmission or severity and duration of illness due to increased</p>	<p>The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks.</p> <p>European Surveillance System (TESSy)²³ – ECDC.</p> <p>Scientific Opinions from EFSA Panel on biological hazards (BIOHAZ).</p>

²² European Surveillance of Antimicrobial Consumption.

http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/database.aspx

²³ The European Surveillance System database.

<http://www.ecdc.europa.eu/en/activities/surveillance/tessy/Pages/TESSy.aspx>

Data required	Detail	Further guidance on resources
	<p>virulence of AMR of pathogens compared to sensitive organisms.</p> <p>Extent of need for antimicrobial treatment (cost), due to interference with first line treatments, treatment failures, availability of alternative treatments, loss of treatment options.</p> <p>Susceptibility of human sub-populations.</p> <p>Horizontal transmission of resistance determinants.</p>	

264 The applicant should provide a discussion that leads to the overall conclusion on the potential adverse
265 health effects of exposure of humans to the hazard(s) and the severity and probability of those
266 consequences occurring.

267 8. Overall qualitative risk estimation

268 The risk estimation integrates the results from the release, exposure and consequence assessments to
269 produce an overall estimate of the risk to public health from antimicrobial-resistant bacteria resulting
270 from the use of the proposed veterinary medicinal product in accordance with its SPC. The risk
271 estimation therefore takes into account the entire risk pathway from the hazard identified to the
272 unwanted outcome. It should be presented as a summary of the key influencing data from each step of
273 the process and a final risk conclusion. Any assumptions and uncertainty that might impact the final
274 risk estimate, or degree of confidence that can be held in it, should be commented upon.
275 Variability under different scenarios (e.g. livestock production systems) should also be briefly
276 addressed. As terms such as high, medium and low are subjective, these should be explained where
277 used.

278 Definitions

279 **Adverse health effect** - An unwanted outcome in humans. Specifically here, this is a human illness
280 due to AMR organisms and determinants in food, or acquired through direct animal contact, as well as
281 increased frequency of infections, treatment failures, loss of treatment options and increased severity
282 of disease manifested by prolonged duration of disease, increased hospitalisation and mortality.

283 **Antimicrobial** - For this guidance, an "antimicrobial" is defined as an active substance of synthetic or
284 natural origin which destroys microorganisms, suppresses their growth or their ability to reproduce in
285 animals or humans. In this context, antivirals, antiparasitics and disinfectants are excluded from the
286 definition.

287 **Antimicrobial resistance** – Antimicrobial resistance is the ability of microorganisms of a certain
288 species to survive or even grow in the presence of a given concentration of an antimicrobial agent that
289 is usually sufficient to inhibit or kill microorganisms of the same species (Directive 2003/99/EC²⁴).
290 Microbiological resistance against an antimicrobial is considered to be present if the Minimum
291 Inhibitory Concentration (MIC) exceeds the epidemiological cut-off value.

292 **Commensal** –An organism is in symbiotic relationship in which one species is benefited while the
293 other is unaffected.

294 **Co-resistance** – [Codex] The ability of a microorganism to multiply or persist in the presence of
295 different classes of antimicrobials due to possession of various resistance mechanisms. [EFSA 2008]
296 Genes conferring AMR are frequently contained in larger genetic elements such as integrons,
297 transposons or plasmids, and as such may be “linked” to other, unrelated resistance genes. In such
298 cases, multiple resistance genes may be transferred in a single event. When two or more different
299 resistance genes are physically linked, this is termed co-resistance. Consequently, selection for one
300 resistance attribute will also select for the other resistance gene(s), termed co-selection.

301 **Co-selection** – refers to the selection of multiple antibiotic resistance genes when one gene is
302 selected. This occurs because the multiple resistance genes are part of the same operon and therefore
303 under control of the same promoter.

304 **Cross-resistance** – [Codex] The ability of a microorganism to multiply or persist in the presence of
305 other members of a particular class of antimicrobial agents or across different classes due to a shared
306 resistance mechanism.

307 **Foodborne commensals** – [VICH GL 27] non-zoonotic bacterial species living in the intestinal content
308 of animals that could be transmitted to humans by the food chain and that normally do not cause
309 foodborne infections in humans.

310 **Foodborne pathogens** – [VICH GL 27] zoonotic organisms of which animals could be carriers in the
311 intestinal content, that could be transmitted to humans by the food chain and subsequently cause
312 food-borne infections in humans.

313 **Hazard** – A hazard is something that is potentially harmful. With respect to antibiotic resistance, the
314 hazards are antibiotic-resistant micro-organisms or their transferable genetic determinants.

315 **Risk** – The probability of an adverse effect and the severity of that effect, consequential to exposure to
316 a hazard.

317 **Risk assessment** – The process of evaluating the risk(s) resulting from a hazard. A risk assessment
318 usually describes the risk in terms of the probability of an unwanted outcome.

319 **Uncertainty** – This reflects a lack of knowledge that can be reduced by additional data or information.

320 **Variability** –The heterogeneity of the subjects modelled, including both randomness and inter-
321 individual variability. Variability cannot be reduced by additional data or information.

322 **Zoonotic bacteria** [WHO, 2004] - Bacteria that are present in animal reservoirs and can be
323 transferred to, and cause infections in, humans.

²⁴ Official Journal of the European Union. Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC. In <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:325:0031:0040:EN:PDF>.

324 References

- 325 Australian Pesticides and Veterinary Medicines Authority. Veterinary Manual of Requirements and
326 Guidelines, Part 10 – Special Data: Antibiotic
327 Resistance. http://www.apvma.gov.au/morag_vet/vol_3/part_10_special.php
- 328 CVMP Strategy on Antimicrobials 2011-
329 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109137.pdf
- 330 EFSA (European Food Safety Authority), 2008. Scientific Opinion of the Panel on Biological Hazards on
331 foodborne antimicrobial resistance as a biological hazard. EFSA Journal. 765, 1-87.
- 332 EMA/CVMP/AWP reflection paper on the risk of antimicrobial resistance transfer from companion
333 animals
334 (EMA/CVMP/AWP/401740/2013). [http://www.ema.europa.eu/docs/en_GB/document_library/Scientific
335 _guideline/2015/01/WC500181642.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500181642.pdf)
- 336 Health Canada, Veterinary Drugs Directorate Guidance for Industry – 2005. Guidance document for
337 microbiological safety studies requirements for preparation of veterinary new drug submissions. Health
338 Canada: http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr-ram_rep-rap_06_05-eng.php
- 339 Official Journal of the European Union. Directive 2003/99/EC of the European Parliament and of the
340 Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council
341 Decision 90/424/EEC and repealing Council Directive 92/117/EEC. In [http://eur-
342 lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:325:0031:0040:EN:PDF](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:325:0031:0040:EN:PDF).
- 343 US Department of Health and Human Services, Food and Drug Administration, Center for Veterinary
344 Medicine, October 23, 2003. Guidance for Industry #152. Evaluating the Safety of Antimicrobial New
345 Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health
346 Concern. [http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry
347 /ucm123614.htm](http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123614.htm)
- 348 VICH GL 27: Guidance on pre-approval information for registration of new veterinary medicinal
349 products for food producing animals with respect to antimicrobial
350 resistance. <http://www.vichsec.org/en/topics.htm#8>
- 351 Vose D, Acar J, Anthony F, Franklin A, Gupta R, Nicholls T, Tamura Y, Thompson S, Threlfall EJ, van
352 Vuuren M, White G, Wegener HC, Costarrica ML. Antimicrobial resistance: risk analysis methodology
353 for the potential impact on public health of antimicrobial resistant bacteria of animal
354 origin. [http://www.codexalimentarius.org/search-results/?cx=018170620143701104933%3Ai-
355 zresgmxec&cof=FORID%3A11&q=antimicrobial&siteurl=http%3A%2F%2Fwww.codexalimentarius.org
356 %2F&sa.x=19&sa.y=9](http://www.codexalimentarius.org/search-results/?cx=018170620143701104933%3Ai-zresgmxec&cof=FORID%3A11&q=antimicrobial&siteurl=http%3A%2F%2Fwww.codexalimentarius.org%2F&sa.x=19&sa.y=9)
- 357 WHO/FAO. Risk Characterisation of Microbiological Hazards in Food: Guidelines, 2009..
- 358