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

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Executive summary

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

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

1. Introduction (background)

The CVMP Strategy on Antimicrobials advises that CVMP will consider available data on antimicrobial resistance (AMR) and give AMR-related risks adequate weight in the benefit-risk assessment when deciding to authorise, or restrict use of, an antimicrobial veterinary medicinal product. In regards to the risk to public health, food has always been regarded as an important route through which human beings may be exposed to antimicrobial-resistant bacteria, and there is now increasing concern in regards to the risk of exposure through direct contact with livestock for certain organisms. Although the VICH GL 27[1] already provides guidance on data requirements for registration of new veterinary medicinal products for food producing animals with respect to AMR, not all aspects of the risk assessment are addressed and there are no recommendations on how the final risk estimation should be concluded. Increasing concern has been raised from many parties in regards to the impact on public health of the use of antimicrobials in animals. Therefore, this guidance on the risk assessment part of the risk analysis process for antimicrobial veterinary medicinal products is aimed to provide a systematic approach to the evaluation of the associated scientific data and to improve the transparency and consistency of the regulatory decision-making process.

2. Scope

The purpose of this guideline is to provide guidance on the data required and the methodology to be applied to the assessment of the risk to public health from AMR in relation to Marketing Authorisation applications and referrals for antimicrobial veterinary medicinal products for use in food producing species.

The risk question to be addressed is:

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

[1] 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

In regards to the risk to human health, this includes a consideration of the consequences of AMR including loss of treatment options, increased disease severity and/or mortality and the increased burden on healthcare services. This should be considered in the context of the community and hospital populations within the EU, with attention to specific vulnerable sub-populations or geographical regions as needed.

The risk assessment should address both the current state of play and, for a new Marketing Authorisation application, the potential change in the risk based on the proposed conditions of use going forwards. It is acknowledged that certain elements of the risk assessment, including emergence of novel resistance mechanisms and change in the importance of the antimicrobial to human health, will be speculative and associated with uncertainty.

The scope of this guidance extends to antimicrobial veterinary medicinal products (VMPs) intended to treat food producing species, and that potentially select resistant bacteria or resistance determinants that may be transmitted through foodstuff of animal origin or by direct contact with the target species and subsequently have an impact on human health.

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

Although there are many other potential routes of human exposure to antimicrobial-resistant bacteria (e.g. via general environmental contamination) it is currently difficult to attribute the resistance to use of VMPs and these routes are not within scope of this guidance. CVMP is developing a separate reflection paper on AMR in the environment. VMPs for companion animals, including horses not intended for human consumption, are also excluded from the scope of this guidance. The EMA/CVMP/AWP has published a reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP/401740/2013)[2].

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

3. Legal basis

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

4. When does this guidance apply?

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

- Any Marketing Authorisation application for an antimicrobial substance not previously authorised for use in a veterinary medicinal product for food producing species in the EU.

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

- Any application for a combination of antimicrobial substances not previously authorised for use in a veterinary medicinal product for use in food producing species in the EU.
- Any application relating to an antimicrobial substance previously authorised for use in a food producing species that could lead to an increase in volume of use or an increased risk to public health, e.g.
    - A change to the dosage form or pattern of use or exposure e.g. a change from individual animal use to group medication; a change in the formulation from injectable to in-feed/in-water medication.
    - Extension to a new major food-producing species.
    - Addition of another major group within the same food-producing species (e.g. beef cattle to dairy cattle).
    - Addition of new major therapeutic indications.
    - Any change to the dosing regimen.
- Referral procedures that include concerns over the AMR risk to human health.

A separate risk assessment should be provided for each formulation/ animal species/ indication/ dosing regimen, although parts of the assessment are common to more than one scenario.

The guidance does not apply for generic applications made under Article 13.1 of the Directive.

For other cases, such as Marketing Authorisation applications for minor species or minor indications, a risk assessment should be provided unless a justification can be given that this will not present a new hazard or significantly increase the exposure to AMR.

5. Methodology for the risk assessment

The risk assessment methodology has been adapted from that that described by the OIE (Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin; Vose et al, 2001[3]; OIE Terrestrial Animal Health Code, chapter 6.10). In addition, note has been taken of the methodology proposed by Codex (Guidelines for risk analysis of foodborne antimicrobial resistance, CAC/GL 77-2011[4]) and the requirements in place in other jurisdictions (FDA[5], Health Canada[6], APVMA[7]). The OIE methodology is used as the basis for this CVMP guidance to facilitate alignment with models used in other regulatory jurisdictions and due to the particular applicability of the "release assessment" step to the risk analysis for VMPs. The methodology takes into account: knowledge of the mechanisms of resistance to the antimicrobial under

[3] 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.
[4] http://www.codexalimentarius.org/search-results/?cx=018170620143701104933%3Ai-zresqmxec&cof=FORID%3A11&q=antimicrobial&siteurl=http%3A%2F%2Fwww.codexalimentarius.org%2F&sa.x=19&sa.y=9
[5] 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
[6] 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
[7] Australian Pesticides and Veterinary Medicines Authority. Veterinary Manual of Requirements and Guidelines, Part 10 – Special Data: Antibiotic Resistance. https://apvma.gov.au/node/1018

consideration; the probability of exposure of zoonotic and commensal bacteria in the target species based on the conditions of use of the veterinary medicinal product under consideration; the probability of subsequent human exposure to AMR via food or direct animal contact and also, as the assessment relates to the risk to human health, the importance of the antimicrobial substance to human medicine and consequences to human health. As the risk assessment is for a specific antimicrobial VMP, more emphasis is placed on the impact of the conditions of use relevant to the product, and less emphasis on aspects that relate to risk factors that are not product-related e.g. impact of methods of food processing on bacterial load in foods.

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

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

Categorisation of risk factors / Assessment scales

It is recognised that there are likely to be substantial data gaps that preclude a quantitative approach to this risk assessment. Consequently, this guidance proposes that a qualitative approach is taken, although, where quantitative data are available applicants are encouraged to refine the approach. A structured and transparent approach should still be taken to the assessment. It is recommended that the key risk factors are assessed as very low (VL), low (L), medium (M) or high (H) relative to the range of possible outcomes. Examples are given in the release, exposure and consequence assessment sections of this guidance. These may be refined by the applicant according to the specific conditions of

use of the product, e.g. species production sub-type, countries where the MA is sought if not a centrally authorised product. An overall categorisation (VL, L, M, H) should be given at the end of each section of the assessment, although it is recognised that the weighting of each contributing risk factor is somewhat arbitrary.

The following categorisation may be used for the release and exposure assessment:

- Very low – very low probability that release/exposure to the hazard can occur (plausible, but very unlikely).
- Low – Low probability for release/exposure to occur.
- Medium – Medium probability for release/exposure to occur (likely, probable).
- High – Significant probability for release/exposure to occur (very likely, certain).

A separate categorisation for the consequence assessment is included at the end of section 7.4.

Uncertainty and variability

The applicant should comment on any assumptions that have been made, especially in relation to data gaps or poor understanding of risk pathways. Uncertainty (due to lack of, or poor quality, data) may be described as low, medium or high. For example:

Low uncertainty – abundant high quality data leading to consistent conclusions.

Medium uncertainty – limited amount of data.

High uncertainty – no data available leading to reliance on expert opinion.

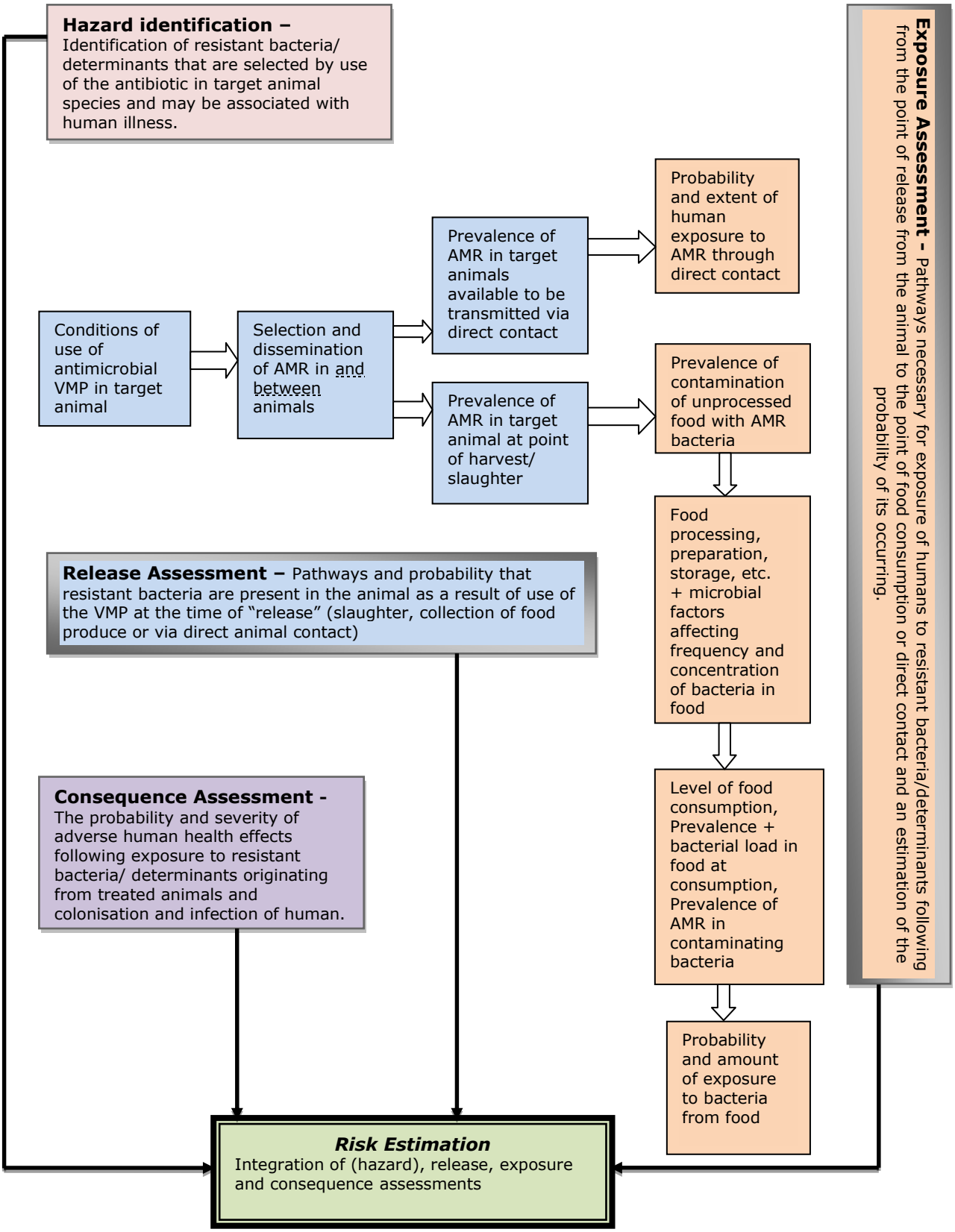
In regards to variability in data (e.g. variation between EU countries in prevalence of resistance), if this is significant an option may be to present scenarios considering best, most common and worst case for the risk factor.

The uncertainty and variability associated with each factor/parameter and the influence these may have on the reliability and generalisability of the overall risk assessment should be evaluated. Within this context, the risk assessor should still aim to provide a clear summary of the available data and conclusion at the end of each step of the assessment.

An example of the risk assessment approach is given in the publication by Alban et al. (2017); although in this case the context was that of use of an established antimicrobial.

The risk assessment should take into account the proposed conditions and anticipated extent of use of the veterinary medicinal product (e.g. target species, indication, route of administration, treatment incidence, see below 7.2) and is therefore specific to those circumstances. By integrating the release, exposure and consequence assessments, the potential risk of the identified hazard(s) should be estimated. An acceptable level of risk is that which when weighed against the proposed benefits of use of the veterinary medicinal product in the target species, will not significantly compromise therapeutic use of antibiotics in humans or human health. Risk management measures to minimise the risk to public health from use of the VMP may also be taken into account. The acceptability of the risk level has to be weighed in the context of the overall benefit-risk as determined from the complete dossier for the product. This aspect is not addressed further here as this guidance document only addresses the risk assessment process. Further guidance on the evaluation of the benefit-risk for VMPs is given in the document: Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products (EMEA/CVMP/248499/2007).

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



6. Data sources and quality

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

When data are not available in public literature or from the sponsor's own studies, then expert opinion may be used. In this case, it is better for the applicant to solicit the views of more than one expert. Where there are complete data gaps, these should be highlighted as areas of high uncertainty.

7. Data requirements

7.1. Hazard identification

This step addresses the identification of antimicrobial-resistant bacteria or resistance determinants that could result in human illness and may be selected due to the use of the antimicrobial substance concerned in the target animal species. Resistance may develop both in bacteria that are zoonotic and/or in commensal bacteria in animals that could pass transferable resistance determinants to other bacteria that are pathogenic in humans. In regards to zoonotic pathogens, attention should be focused on those for which the concerned antimicrobial/class is a recognised treatment in human medicine in the EU. For the purpose of this risk assessment, only bacteria that are foodborne or may be transferred by direct contact with animals need to be considered. A non-exhaustive list is given in Annex 1.

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: • Foodborne pathogens (e.g. *Campylobacter, Salmonella*); • Bacteria that could be transmitted by direct contact (e.g. *Staphylococcus*	See VICH GL27, section 1.3. In addition consider bacteria that may be transmitted by direct contact.

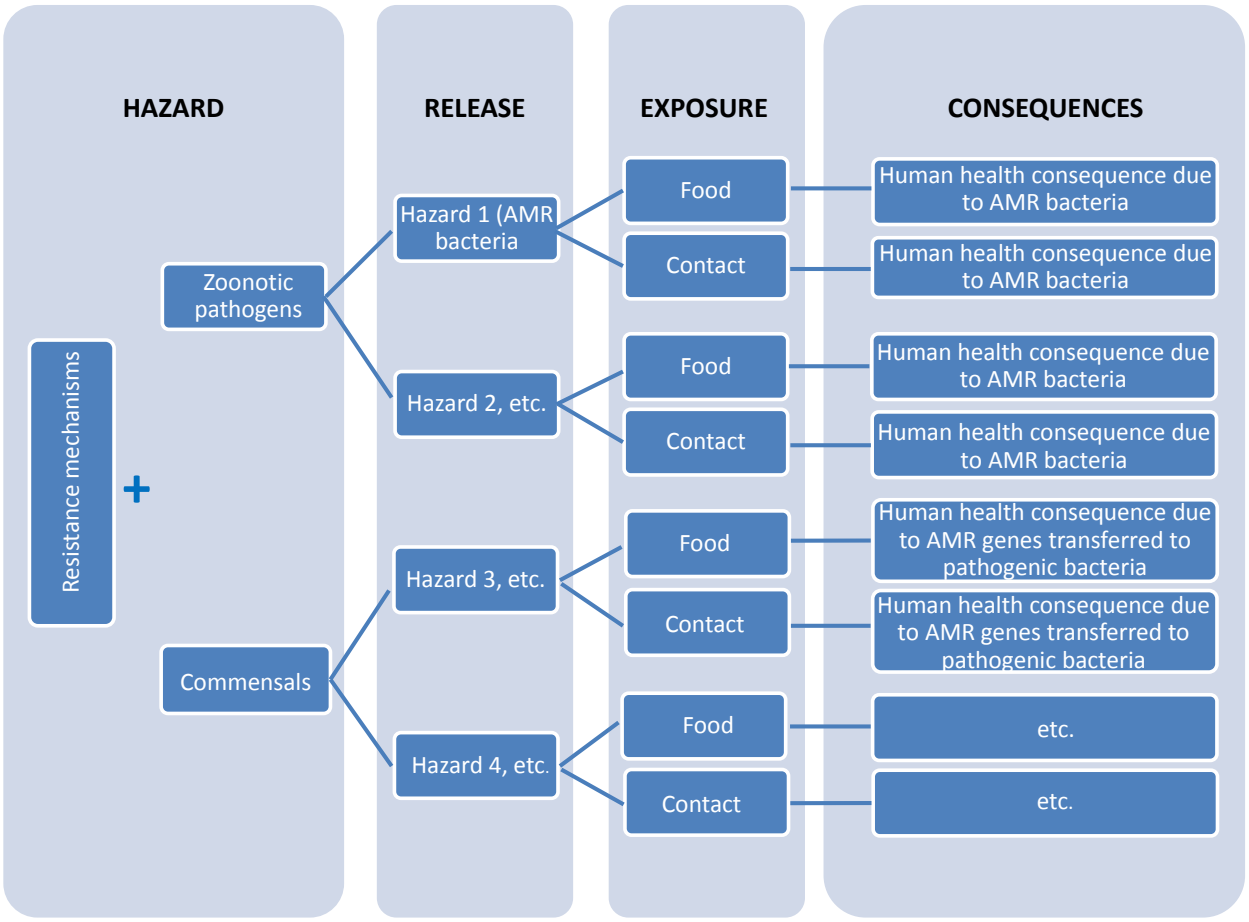
Data required	Detail	Further guidance on resources
	aureus); • Indicator/commensal bacteria that may carry mobile resistance determinants that could be passed to human pathogenic bacteria (e.g. *Escherichia coli, Enterococcus* spp).	
Resistance mechanisms associated with the antimicrobial in animal and human bacteria.	E.g. antimicrobial inactivation, alteration of target, efflux pumps.	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.
Genetic basis of resistance – • Intrinsic	Presence of any intrinsic resistance genes which may be expressed under certain circumstances either constitutively or inducibly.	
• Acquired – chromosomal (mutational) or acquisition of resistance determinants	Whether resistance is related to chromosomal mutation or acquisition of mobile genetic elements (such as plasmids) carrying the resistance determinant, or may be related to both.	
Location of resistance determinants	e.g. chromosomal, plasmid, transposons including information on whether resistance is transferred vertically and/or horizontally. Association of resistance determinants with mobile genetic elements.	
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

Data required	Detail	Further guidance on resources
		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 breakpoints and epidemiological cut-off values (ECOFFs) should be considered in the assessment.	See VICH GL 27, section 1.3

The applicant should provide a discussion that leads to an overall conclusion on the opportunity for selection of antimicrobial-resistant bacteria /determinants that could result in resistant infections in humans, and may be selected due to the use of the concerned antimicrobial substance in the target animal species. This discussion should focus on the interaction of the antimicrobial with the individual identified pathogens and commensals together with their associated resistance mechanism/ genes, and considering:

- intrinsic or acquired resistance
- location of resistance determinants and whether resistance is transferred vertically and/or horizontally
- the possibility of co- and cross-selection of resistance to other antimicrobials
- the presence of resistance determinants in the EU; consideration of determinants known to exist in third countries or in other microbiomes such as in waste water

For each hazard identified, the release, exposure and consequence assessments are then mapped forwards individually, for example:



7.2. Release assessment

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

282 **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, estimate of usage	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[8], ESVAC[9] data on PCU for the target species[10] e.g. High – pigs, cattle, poultry Medium – small ruminants Low – fish, horses Very low - rabbits The categorisation above may be used as a starting point and may be refined according to the specific conditions. 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 for substance (and species/production category, if available). 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.

[8] Eurostat is the statistical office of the European Union.
http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/
[9] The European Surveillance of Antimicrobial Consumption.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp
[10] 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 For the purpose of this guideline, high is > 10,000 PCU, medium >5,000 – 10, 000, low > 1,000 – 5,000, very low < 1,000.

Data required	Detail	Further guidance on resources and interpretation of data
PK and PD of the antimicrobial	ADME[11] in the target animal species. PD: impact on zoonotic and commensal flora. Concentration- , time- or co-dependent effects, PAE[12], Minimal Selective Concentration and sub-MIC[13] effects etc. PK/PD[14] in respect of bacterial species identified as potential hazards to human health, if available.	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). See VICH GL 27, section 1.
Occurrence and rate of transfer of resistance determinants	Studies may be included to demonstrate both *in vitro* or *in vivo* rate and extent of resistance selection. This may include studies conducted in laboratory animals or the target species, and *in vitro* mutation frequency studies. Can resistance determinants be transferred horizontally between bacteria and to bacteria of different species (transformation, transduction, conjugation) and at what rate? Do findings from *in vitro* conditions reflect field situation?	See VICH GL 27, sections 1.5 and 2.1 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)[15].
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.	See VICH GL 27, section 2.2. 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. Higher risk would be associated with antimicrobial concentrations ranging within the selective window for relevant organisms of the microbiome.

[11] ADME: absorption, distribution, metabolism, excretion.
[12] PAE: post antibiotic effect
[13] MIC: minimal inhibitory concentration
[14] PK/PD: pharmacokinetics/pharmacodynamics
[15] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf

Data required	Detail	Further guidance on resources and interpretation of data
Prevalence of carriage of zoonotic bacteria and commensals in target animal population and baseline prevalence of resistance in those bacteria.	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. In relation to direct contact, literature studies may be available on meat and skin carriage of relevant bacteria in the target species and prevalence in the immediate farm environment.	E.g. The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks (EFSA/ECDC).[16] In consistency with EFSA, the following ranking may be used for the proportion of positive sample units or prevalence of zoonotic agents: high >20%, medium >10% to 20%, low >1% to 10%, v. low ≤1% The European Union Summary Report on Antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union (EFSA/ECDC)[17] Other sources may also be used, e.g. CEESA.[18] In consistency with EFSA, the percentage of resistant isolates as a proportion of those tested may be expressed as: high > 20%, medium > 10% to 20%, low > 1% to 10% or v. low ≤ 1%
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.

283 The applicant should assess whether the evidence relating to each factor points towards high, medium,
284 low or very low (H, M, L, VL) probability of favouring resistance emergence in relative terms for each
285 identified hazard. An indication of the categorisation for some factors is given in the table above
286 ('interpretation of data').

287 The applicant should provide a discussion that leads to the overall conclusion on the probability (H, M,
288 L, VL) that antimicrobial-resistant bacteria/determinants will be selected for and "released" as a result

[16] http://www.efsa.europa.eu/en/topics/topic/monitoringandanalysisoffood-bornediseases.htm?wtrl=01
[17] http://www.efsa.europa.eu/en/topics/topic/amr.htm
[18] The European Animal Health Study Centre (CEESA): European Antimicrobial Susceptibility Surveillance in Animals Programme (EASSA).

of the proposed use of the product in animals, together with an indication of the uncertainty (H, M, L) and variability (see section 5).

7.3. Exposure assessment

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

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

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[19] /Eurostat, FAO-OECD[20] High (> 20 kg per capita p.a.) – pork, poultry, fish meat Medium (>10-20 kg per capita p.a.) – beef/veal Low (> 1-10 kg per capita p.a.) – sheep meat V low (< 1 kg per capita p.a.)
b) Prevalence of food contamination at point of consumption with bacteria relevant to the hazard (excluding produce imported from outside EU).		EFSA/ECDC Zoonosis reports. Data may also be provided on extent of secondary contamination due to food processing, handling etc. which would be excluded for the purpose of this risk assessment
c) Microbial load of food at point of consumption		

[19] http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm
[20] https://data.oecd.org/agroutput/meat-consumption.htm

Data required	Detail	Further guidance on resources
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) Data from source attribution studies	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. *The EFSA Journal* (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; human prevalence surveys.		A distinction between professional contact (occupational hazard reports) and occasional contact (e.g. children on farm visits) might be indicated. Studies may be available demonstrating levels of human carriage or colonisation with resistant bacteria.

The applicant should provide a discussion that leads to the overall conclusion on the amount of exposure of humans to antimicrobial-resistant organisms/determinants via food at the point of consumption or through direct contact, and the probability of its occurring. The categorisation of the exposure (H, M, L, VL) can be used, together with an indication of the uncertainty (H, M, L) and variability (see section 5).

7.4. Consequence assessment

This step addresses the potential consequences (adverse health effects on the individual and burden on healthcare services) of exposure of humans to each of the hazard(s) in the EU and the severity and probability of the consequences occurring.

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

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

[21] http://www.efsa.europa.eu/en/efsajournal/pub/764.htm

322 Consideration should be given to community and hospital populations, with attention to specific
323 vulnerable sub-populations or geographical regions as needed.

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

Data required	Detail	Further guidance on resources
a) Relative importance of the antimicrobial to human medicine	Spectrum of activity and important disease indications (including target pathogens) for use in humans. Availability of alternative antimicrobial treatments. Extent of use in human medicine.	See published background information to the AMEG's categorisation of antimicrobials - scientific advice to be finalised in 2019. ESAC database[22]
b) Dose-response relationships (where available)	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.	
c) Consequences of AMR in human infections	Number of cases of human infection reported (and estimate of unreported cases) per annum. Number/proportion of cases attributed to animal food produce/animal contact. Severity of disease: deaths, long term impacts, number of days illness, hospitalisation (length of stay, additional treatment). Prevalence of antimicrobial resistance in human isolates and attribution to animal source (where possible).	The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks. European Surveillance System (TESSy)[23] – ECDC. Scientific Opinions from EFSA Panel on biological hazards (BIOHAZ).

[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
	Any increase in transmission or severity and duration of illness due to increased virulence of AMR of pathogens compared to sensitive organisms. Extent of need for antimicrobial treatment (cost), due to interference with first line treatments, treatment failures, availability of alternative treatments, loss of treatment options. Susceptibility of vulnerable human sub-populations. Horizontal transmission of resistance determinants.	

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

The following categorisation may be used:

Very low – The antimicrobial is of very low importance in terms of the frequency of use to treat a disease for which alternatives are commonly available and the outcomes due to resistant organisms are not different.

Low - The antimicrobial is of low to medium importance in terms of the frequency of use to treat a disease for which the outcomes are more serious with impact on the individual and on healthcare services.

Medium - The antimicrobial is of medium to high importance in terms of the frequency of use to treat a disease for which the outcomes are more serious with impact on the individual and on healthcare services, requiring (possibly prolonged) hospitalisation.

High - The antimicrobial is a last resort treatment (or one of few alternatives) for a disease for which the outcome of treatment failure is very severe requiring lengthy hospitalisation or resulting in disability or death.

Alternatively, as a **pragmatic approach**, the consequence assessment can be based on a combination of (i) the AMEG categorisation for the substance/class and (ii) the extent of use of the class in human medicine in the EU. For hospital use this should be reported preferably as DDD per 1000 patient days or DDD per 1000 admissions, and for community use it should be reported as DDD per 1000 inhabitants per day, if these data are available. Annex 2 gives an indicative categorisation based on European consumption data for 2016, obtained courtesy of ESAC-Net.

The ranking for the consequence element is then derived according to the matrix below:

AMEG category	Extent of use in human medicine			
	Very low	**LOW**	**MEDIUM**	**HIGH**
3	High	High	High	High
2	High	High	High	High
2/1	Low	Medium	Medium	High
1	Very low	Low	Low	Medium

This table will be subject to revision and finalised after the AMEG scientific advice is completed.

8. Overall qualitative risk estimation

The risk estimation integrates the results from the release, exposure and consequence assessments to produce an overall estimate of the risk to public health from antimicrobial-resistant bacteria resulting from the use of the proposed veterinary medicinal product in accordance with its SPC. The risk estimation therefore takes into account the entire risk pathway from each of the hazards identified to the unwanted outcomes. It should be presented as a summary of the key influencing data from each step of the process and a final risk conclusion. Any assumptions and uncertainty that might impact the final risk estimate, or degree of confidence that can be the held in it, should be commented upon. Variability under different scenarios (e.g. livestock production systems, geographical regions) should also be briefly addressed where relevant.

Definitions for the purpose of this guideline

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

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

Antimicrobial resistance – Antimicrobial resistance is the ability of microorganisms of a certain species to survive or even grow in the presence of a given concentration of an antimicrobial agent that is usually sufficient to inhibit or kill microorganisms of the same species (Directive 2003/99/EC[24]).

Clinical breakpoint – For definition please refer to EUCAST: http://www.srga.org/Eucastwt/eucastdefinitions.htm

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

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

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

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

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

Hazard – A hazard is something that is potentially harmful. With respect to antimicrobial resistance, the hazards are antimicrobial-resistant bacteria or their transferable genetic determinants.

[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.

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

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

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

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

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

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Annex 1

Zoonotic and commensal bacteria present in different food-producing species in which carriage of AMR could be a hazard to human health (non-exhaustive):

Bacterial species	**Routes of exposure**	**Animal species that are possible sources**
Zoonotic bacteria		
Campylobacter spp e.g. *jejuni, coli*	**Food** (meat, milk) (Contact)	**Poultry** (jejuni) Pigs (coli, jejuni) Cattle Sheep, goats Fish
Salmonella spp	**Food** (meat, eggs, milk) Contact	**Pigs** (Typhimurium) **Poultry** (Infantis, Enteritidis) Cattle (Typhimurium, Dublin) Sheep, goats Horses Fish
Leptospira hardjo	Contact	**Cattle**
Coxiella burnetii[1]	Contact, local environment. (Food - milk)	Cattle Sheep, goats
Staphylococcus aureus including MRSA	Contact (Food - milk)	Pigs Poultry Cattle Horses
Brucella spp	**Contact** Food (milk)	Cattle (abortus) Sheep, goats (melitensis) (Pigs) (suis)
Bacillus anthracis	**Contact**	Cattle, sheep, goats, pigs, horses
Chlamydia psittaci	Contact	Sheep Poultry
Pasteurella multocida	Contact	Pigs, cattle, poultry

Streptococcus suis Other zoonotic streptococci (e.g. *S. equi subsp. zooepidemicus*)	Contact	Pigs Other species.
Vibrio parahaemolyticus, V. vulnificus *Mycobacterium marinum* *Aeromonas hydrophila*	Food Contact	Fish Vibrio are not included for other spp as they are primarily food contaminants from aqueous / marine environments.
Commensals (indicator organisms)		
E coli	Food Contact	All
Enterococcus faecalis, faecium	Food Contact	All
Aeromonas hydrophila	Food, contact	Fish

[1]*Coxiella burnetii* is an obligate intracellular pathogen. Results of *in vitro* susceptibility testing (requiring specialised methods) have been described in the scientific literature. It is accepted that the available literature is not extensive (Kersh, G.J. 2013).

Annex 2

Consumption of antibacterials for systemic use (DDD per 1000 inhabitants per day), ambulatory care sector (AC, data from 29 countries) and hospital sector (HC, data from 23 countries) combined, EU/EEA, 2016. Based on data provided courtesy of ESAC-Net.

Antibacterial class	**ATC code**	**Consumption** (DDD per 1000 inhabitants per day)	**Categorisation** (as provided by CVMP)*
Tetracyclines, incl. glycylcyclines	J01AA	60.30	M
Amphenicols	J01BA	0.08	VL
Penicillins with extended spectrum	J01CA	121.22	H
Beta-lactamase sensitive penicillins	J01CE	24.68	M
Beta-lactamase resistant penicillins	J01CF	12.57	L
Combinations of penicillins, incl. beta-lactamase inhibitors	J01CR	153.38	H
1st- and 2nd-generation cephalosporins	J01DB, J01DC	55.27	M
3rd- and 4th-generation cephalosporins	J01DD, J01DE	13.55	L
Monobactams	J01DF	0.04	VL
Carbapenems	J01DH	1.83	L
Sulfonamides and trimethoprim, incl. combinations	J01EA to J01EE	17.58	L
Macrolides	J01FA	74.99	M
Lincosamides	J01FF	8.79	L
Streptogramins	J01FG	0.89	VL
Aminoglycoside antibacterials	J01GA, J01GB	2.58	L
Quinolone antibacterials	J01MA, J01MB	55.92	M
Glycopeptide antibacterials	J01XA	1.03	L
Polymyxins	J01XB	0.72	VL
Steroid antibacterials	J01XC	0.25	VL
Imidazole derivatives	J01XD	2.03	L
Nitrofuran derivatives	J01XE	18.17	L

*VL (very low), <1.0; L (low), 1.0 to <20.0; M (medium), 20.0 to 100, H (high), >100 DDD per 1000 inhabitants per day.