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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 animal species

Final

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Executive summary

This guideline provides advice in regard to applications for marketing authorisations and variations, referrals and post-authorisation studies, as relevant for antimicrobial veterinary medicinal products (VMPs) on the data required and the methodology to be used for performing an assessment of the anticipated risk to public health from antimicrobial resistance (AMR) due to use of the product. The scope of the guidance is applicable to VMPs intended for food-producing animal species.

The risk assessment methodology is adapted from that described by the World Organisation for Animal Health (WOAH) (OIE, 2018). Other relevant methodologies, such as that of Codex Alimentarius (Codex Alimentarius, 2011), were also considered for the preparation of this guidance (see section 5). The steps required in the risk assessment take into account: the identification of resistant zoonotic bacteria or resistance determinants that could be associated with bacteria causing human illness that are selected by the use of the antimicrobial VMP in animals (hazard identification); the pathways leading to exposure of zoonotic and commensal bacteria to the antimicrobial in the target species, based on the conditions of use of the VMP under consideration (release assessment); the subsequent human exposure to AMR from animal food produce or animal contact (exposure assessment); and the resulting consequences to human health (consequence assessment).

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 resulting from the use of the antimicrobial VMP.

According to Regulation (EU) 2019/6 ('the Regulation') (Official Journal of the European Union, 2019), the definition of 'antimicrobial' includes antibiotics, antivirals, antifungals and anti-protozoals. This guideline has been developed primarily for antibiotics but the principles thereof could be applied at high level to other types of antimicrobial substances.

1. Introduction (background)

The Regulation indicates that any risk relating to the development of AMR must be taken into account in the benefit-risk assessment (Article 4(19)) leading to the decision to authorise an antimicrobial VMP. Further, as part for the application for marketing authorisation (or -as appropriate- variation), information about risk mitigation measures to limit AMR development linked to the use of the product should be provided, and that subsequent risk mitigation measures should be applied (Article 8(2)(b)). In respect of 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 regard to the risk of exposure through direct contact with livestock for certain organisms. Although VICH GL 27 (EMEA/CVMP, 2004) already provides guidance on data requirements for registration of new VMPs for food-producing animal species 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 regarding 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 VMPs 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 initial marketing authorisation and variation applications, as well as relevant post-marketing obligations and referrals, for antimicrobial VMPs for use in food-producing animal species.

VMPs for companion animals, are 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, 2015).

The risk question to be addressed is:

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

In regard to the risk to human health, this includes a consideration of the consequences of AMR, such as loss of treatment options, increased disease severity and/or mortality, which leads to an increased burden of disease. 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 application (either for a new marketing authorisation or as a variation to an existing one), the potential change in the risk based on the proposed conditions of use. Related to the transmission of AMR both, the foodborne route and direct contact with treated food producing animals should be taken into account. 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 theoretical and associated with uncertainty. The assessment of AMR risks to humans via the environment originating from the use of VMPs, that is the environment acting as a potential vehicle for spreading the risk of AMR to humans, is not addressed by this GL.

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 VMP in question and the specific conditions of its use, where relevant. Use outside the terms proposed for the marketing authorisation does not have to be considered within the risk assessment.

As indicated above, according to the Regulation, 'antimicrobial' includes antibiotics, antivirals, antifungals and anti-protozoals. This guideline has been developed primarily with antibiotic substances in mind, but in principle the structure could be applied at high level to inform on the risk to public health from other antimicrobial products as well.

Article 37(5) of the Regulation allows for the designation of (groups of) antimicrobials to be reserved for the treatment of certain infections in humans and it is stated in Article 37(3) that marketing authorisations for products containing these substances shall be refused. Hence this guideline is not applicable to intended VMPs containing these antimicrobials[1].

[1] Available in the Annex of Commission Implementing Regulation (EU) 2022/1255.

3. Legal basis

Article 8(2) of the Regulation requires that an application for a marketing authorisation for an antimicrobial VMP should include 'documentation on the direct or indirect risks to public or animal health or to the environment of use of the antimicrobial veterinary medicinal product in animals' and 'information about risk mitigation measures to limit antimicrobial resistance development related to the use of the veterinary medicinal product'. This provision is also applicable to certain variations as Article 62(2), which lays out the requirements for variations requiring assessment - cross-refers to the data referred to in Article 8 that are relevant to the variation. In particular, applications for variations aiming at the addition of a new strength with impact on the dosage regimen, pharmaceutical form, route of administration, dosage regimen, target species or indication should contain the information requested under Article 8(2).

This guideline should be read in conjunction with requirements laid out in Annex II to the Regulation, including the specific requirements for specific types of marketing authorisations as provided for in Section IV of Annex II.

The 3Rs principles (replacement, reduction and refinement) should be applied when conducting animal studies as set out in Annex II to Regulation (EU) 2019/6.

4. When does this guidance apply?

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

- Any marketing authorisation application for VMPs containing an antimicrobial substance for use in food-producing animal species in the EU.
- Any application for a combination of antimicrobial substances (or a combination that includes at least one antimicrobial substance) for use in a VMP for food-producing animal species in the EU.
- Post-authorisation product development (submitted as a variation requiring assessment under Article 62 of the Regulation) relating to an antimicrobial substance previously authorised in a VMP for use in a food-producing animal species that may lead to an increased risk to public health, e.g.:
    - A change of the pharmaceutical form, administration route and/or dosage regimen or changes in strength with an impact on the dosage regimen.
    - Variations to add a new food-producing animal species.
    - Addition of a subcategory of the same food-producing animal species (e.g. beef cattle, where for that product only dairy cattle has been authorised as a subcategory).
    - Addition of new therapeutic indications.
    - Referral procedures that include concerns over the AMR risk to human health.
    - Post-authorisation studies required under Article 36(2) to ensure that the benefit-risk balance remains positive given the potential development of antimicrobial resistance.
    - Any other post-authorisation measure that may be required and which implies an assessment of the risk of development of antimicrobial resistance for antimicrobial VMPs intended for food-producing animal species.

A separate risk assessment should be provided for each pharmaceutical form, route of administration, animal species and respective subcategories, indication, dosage regimen, changes in strength with an

impact on the dosage regimen, although parts of the assessment will be common to more than one scenario.

Given the tailored dossier requirements for specific marketing authorisation applications provided by Section IV of Annex II to the Regulation, the detailed guidance provided in this document does not apply to generic applications made under Article 18 of the Regulation. The specific requirements in Annex II, Section IV.1.3 for bibliographic information about the level of AMR applies to such applications.

This guideline may also assist applicants for Scientific Advice requesting a Preliminary Risk Profiling (PRP) of an antimicrobial during early stages of product development (EMA/CVMP/CHMP, 2019b); although the PRP is based on a more limited data set and is intended to provide an early indication to future marketing authorisation applicants of the need for risk management measures to be applied to their proposed product.

5. Methodology for the risk assessment

The risk assessment methodology has been adapted from WOAH (OIE, 2018; Vose et al., 2001). In addition, note has been taken of the methodology proposed by Codex (Codex Alimentarius, 2011) and the requirements in place in other jurisdictions (APVMA, 2018; FDA, 2023; Health Canada, 2005). The WOAH 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 consideration; the exposure to the antimicrobial of zoonotic and indicator commensal bacteria in the target species based on the conditions of use of the VMP under consideration; the 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 in the presence of resistance. 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 elements[2] that are not product-related e.g. impact of methods of food processing on bacterial load in foods.

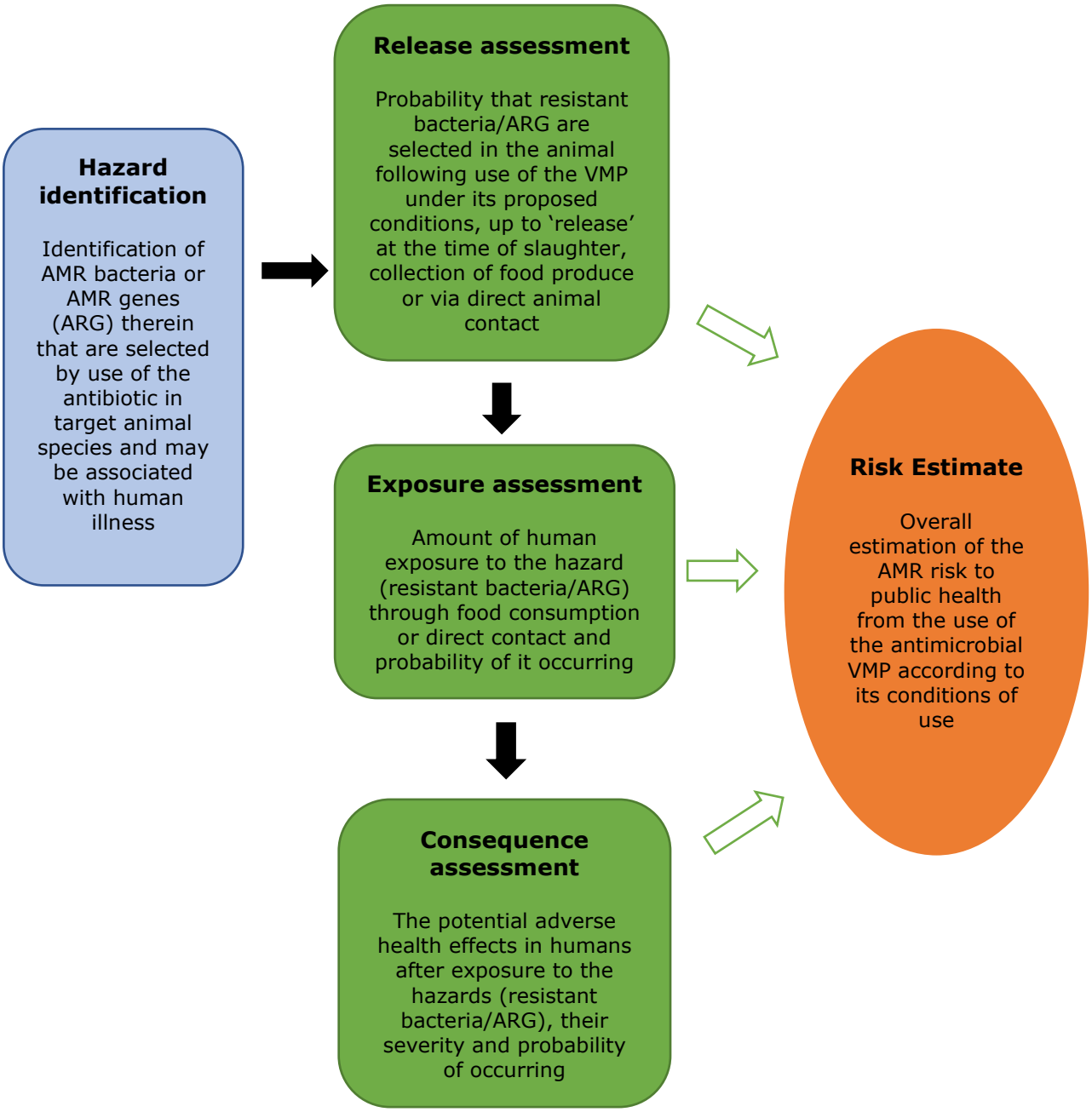
The following steps in the risk assessment structure (Figure 1) should be followed:

- **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 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 VMP in the target species and selection of resistant bacteria in the animal due to this use up to the time of "release" of the identified hazards 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 animal contact, and an estimation of the amount of exposure and probability of its occurring.

[2] 'Risk elements' are the individual parameters/elements that make up each step of the risk assessment and contribute to the size of the overall risk estimate.

- The division of the risk assessment into "release" and "exposure" components effectively separates animal and animal treatment elements that are associated with use of the specific VMP (release) from food-chain and human-related elements (exposure).
- **Consequence Assessment**: The potential consequences (adverse health effects) of exposure of humans to the hazard and the severity and estimated probability of the consequences occurring. The consequence assessment for resistant bacteria may be informed by that for non-resistant organisms; it relates to consequences over and above those caused by an antimicrobial-sensitive strain of a pathogen 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 estimated risk associated with the hazard(s) identified at the outset. The risk estimation therefore takes into account the entire risk pathway from the hazard(s) identified to the unwanted outcome.

Figure 1: Components of the AMR risk assessment to human health from a VMP intended for use in food-producing animal species



Categorisation of risk elements and the outcome for each step of the assessment (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 make refinements. A structured and transparent approach should still be taken to the assessment. It is recommended that the key risk elements 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 VMP, e.g. target species (subcategory) species, indication, route of administration, countries where the marketing authorisation is sought if not a centrally authorised product. An overall categorisation (very low, low, medium or high) should be given at the end of each step/section of the assessment, although it is recognised that the weighting of each contributing risk element is somewhat theoretical.

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

- 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 (see definitions)

The applicant should justify 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 qualitatively as low, medium or high. For example:

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

Medium uncertainty – limited amount of data; extrapolation may have been made to make estimations from data derived under different conditions.

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

Further information on Uncertainty Analysis is available in scientific guidance from EFSA (2018).

In regard 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 element.

The uncertainty and variability associated with each element of each risk assessment step should be identified and reported where this affects the assessment outcome. Within this context, the aim is to provide a clear summary of the available data and conclusion at the end of each step of the assessment, along with the qualitative description of the level of uncertainty and the key elements contributing to this. A final summary of the potential impact of uncertainty and variability on the reliability and generalisability of the overall risk assessment should be provided.

Options for the assessment

Exposure to AMR through both the foodborne and direct contact routes (relates to exposure through handling animals or animal-derived food produce 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) should be addressed. Annex 1 suggests the routes of exposure (food or direct contact) for certain bacteria that are potential hazards. If it can be justified that one route of exposure is highly dominant for a specific hazard (e.g. foodborne route for resistant *Salmonella* spp.), then the risk assessment for that hazard may be conducted considering this route alone.

Provided that the level of certainty for consistent conclusions is high, it may be possible to implement steps of the risk estimate matrix (section 8), the goal being to ensure that adequate data are available to conclude on the overall risk estimate with sufficient certainty that allows effective and proportionate risk mitigation. Where a consequence assessment alone shows that there can be no impact on human health, then the remainder of the risk assessment does not need to be completed. Specifically, this might apply to certain non-antibacterial antimicrobials.

Context in the overall benefit-risk assessment

The risk assessment should consider the proposed conditions and anticipated extent of use of the VMP (e.g. target species (subcategory), indication, route of administration, treatment incidence, see section 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. To determine an acceptable level of risk, the potential detrimental effect on therapeutic use of the antimicrobial in human health has to be balanced against the proposed benefit of the use of the VMP in the target species. Specific risk management measures to minimise the risk to public health from use of the VMP that is the subject of the application have also been taken into account. The acceptability of the risk level is finally 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: 'Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products' (EMA/CVMP, 2024).

Products containing fixed-combinations of antimicrobials

Products may contain more than one antimicrobial in combination, for example in order to treat polymicrobial infections, to take advantage of synergism or to decrease the emergence of resistance. Antimicrobials may also be combined with other molecules (e.g. beta-lactamase inhibitors) in order to overcome a resistance mechanism. The final risk estimation should address the fixed-combination product as intended for use. Suitable data should be provided with this in mind and according to the rationale for the combination. For example, where there is no interaction between two antimicrobial substances and they have different spectra of activity, the risk assessment process could be followed separately for each substance/hazard identified. However, if there is an interaction between the substances, then this should be taken into account for each element of the risk assessment where relevant and possible (e.g. impacts on PK/PD, prevalence of resistance, human health consequences).

6. Data sources and quality

Sources of information include, for example, data presented in other sections of the marketing authorisation dossier (e.g. pharmacodynamics, residues), information from national and EU databases made available by EMA (EMA, 2023), EFSA (EFSA, 2024b) and ECDC (ECDC, 2024), 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 be conducted in compliance with 3Rs principles and (ideally) Good Laboratory Practices (GLP) and/or Good Clinical Practices (GCP), as applicable. For Minimum Inhibitory Concentration (MIC) studies, data for key organisms should be consistent with the requirements in VICH GL 27 (EMEA/CVMP, 2004) and where originating from surveillance programmes, these should be relevant to the EU and should not be older than 5 years.

The quality of the scientific evidence available for the assessment should be considered and commented upon considering the transparency, accuracy and completeness of reporting for different types of research. Critical assessment of research evidence involves evaluating the quality and validity of the study, as well as whether the study is applicable to the current risk assessment question.

For new antimicrobial substances that have not previously been used within the EU, 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. For example, for an application concerning a novel aminoglycoside, reference could be made to data on mechanisms and levels of resistance to other aminoglycosides, with a justification for their relevance based on whether the mechanisms (e.g. specific acetyl transferase enzymes) are likely to confer cross-resistance to the novel molecule.

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.

The information in the tables below under the column headed 'Further guidance on resources' is intended to provide examples, only, and applicants may use additional or alternative data sources.

7. Data requirements

7.1. Hazard identification

This step addresses the identification of antimicrobial-resistant bacteria or resistance determinants that could be associated with human illness and may be selected due to the use of the antimicrobial substance concerned in the target 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 regard 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 (information in this column is given for illustration purposes and is not exhaustive; other resources may be used as appropriate)
Antimicrobial substance-specific information	Antimicrobial class	See VICH GL 27, section 1.1(EMEA/CVMP, 2004)
	Mechanism of action	See VICH GL 27, section 1.2(EMEA/CVMP, 2004)
	Spectrum of activity	See VICH GL 27, section 1.3(EMEA/CVMP, 2004)

Data required	Detail	Further guidance on resources (information in this column is given for illustration purposes and is not exhaustive; other resources may be used as appropriate)
Taking into account the target species (subcategory) 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* spp., *Salmonella* spp.); • Bacteria that could be transmitted by direct contact (e.g. *Staphylococcus aureus*); • Indicator commensal bacteria that may carry mobile resistance determinants that could be passed to human pathogenic bacteria (e.g. *Escherichia coli, Enterococcus* spp).	See VICH GL27, section 1.3.(EMEA/CVMP, 2004) In addition, consider bacteria that may be transmitted by direct contact.
Resistance mechanisms associated with the antimicrobial in animal and human bacteria	E.g. antimicrobial inactivation, alteration of target, efflux pumps. Mechanisms identified in the EU and internationally should be included.	See VICH GL 27, section 1.4(EMEA/CVMP, 2004). 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' (EMA/CVMP, 2016) • criterion B, regarding the risk of transmission of resistance, as defined in the Annex of Commission Delegated
Genetic basis of resistance – • Intrinsic • Acquired – chromosomal (mutational) or acquisition of resistance determinants	Presence of any intrinsic resistance genes which may be expressed under certain circumstances either constitutively or inducibly. 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.	

Data required	Detail	Further guidance on resources (information in this column is given for illustration purposes and is not exhaustive; other resources may be used as appropriate)
		Regulation (EU) 2021/1760[3].
Location of resistance determinants	E.g. chromosomal, plasmid, transposons, gene cassettes, 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 (EMEA/CVMP, 2004). 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' (EMA/CVMP, 2016) • criterion B regarding the risk of transmission of resistance, as defined in the Annex of Commission Delegated Regulation (EU) 2021/1760[3].
Susceptibility data (MIC distribution /MBC) for the	MIC values should be determined with validated	See VICH GL 27, section 1.3(EMEA/CVMP, 2004).

[3] An outcome of this evaluation for antibiotics can be consulted in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in its most recent version - Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans EMA/CVMP. (2022). *Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans - in relation to implementing measures under Article 37(5) of Regulation (EU) 2019/6 on veterinary medicinal products (EMA/CVMP/678496/2021-rev)*. https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/ema_advice_on_designation_of_antimicrobials_reserved_for_human_use_-_report_-_rev_en.pdf. .

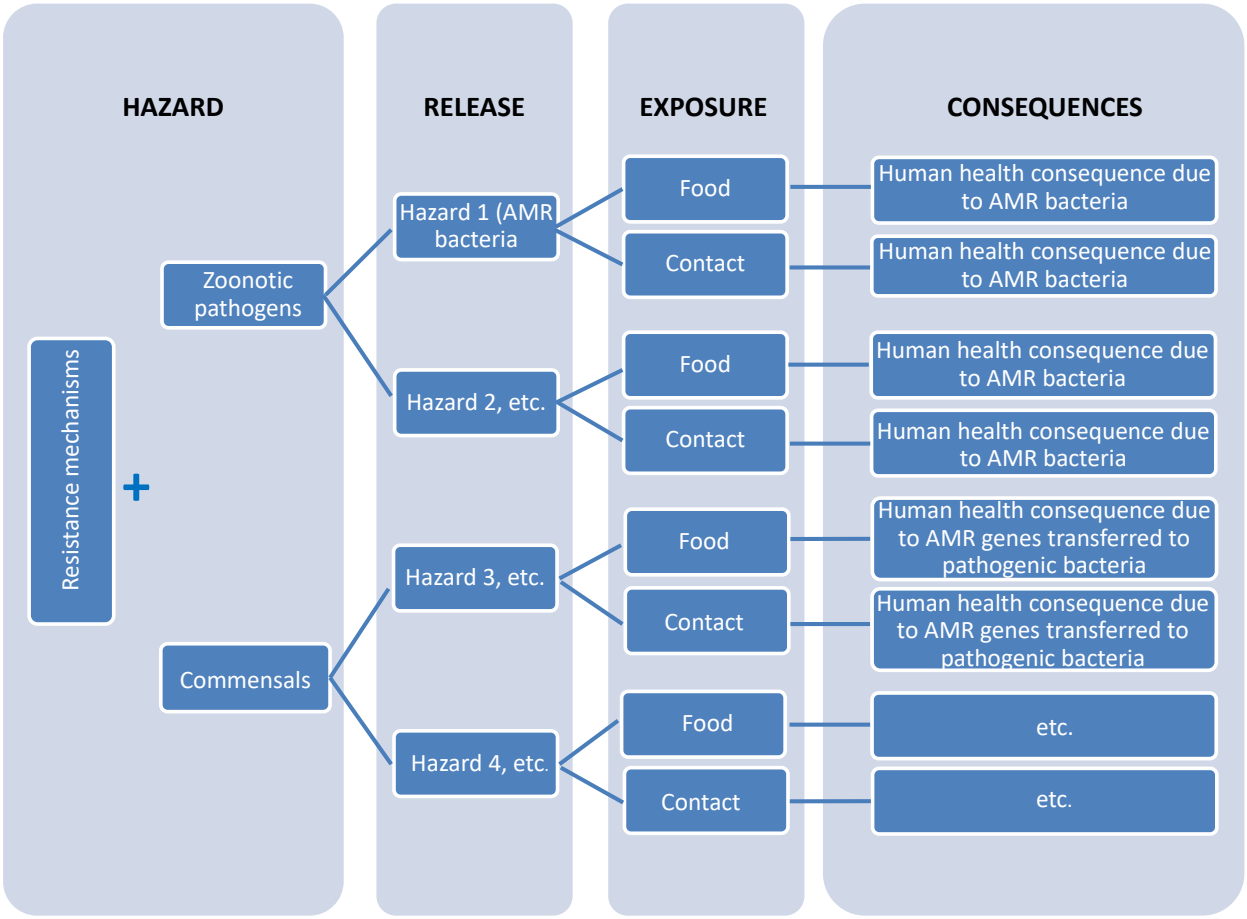
Data required	Detail	Further guidance on resources (information in this column is given for illustration purposes and is not exhaustive; other resources may be used as appropriate)
bacteria of human health concern	methods, where possible. Clinical breakpoints and epidemiological cut-off values (ECOFFs) should be considered in the assessment. Data should be relevant to the EU situation.	

The applicant should provide a discussion that leads to an overall conclusion on the possibility 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 species (subcategory) species. This discussion should focus on the interaction of the antimicrobial with the individual identified pathogens and indicator commensal bacteria together with their associated resistance mechanisms/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 antimicrobial substances. In cases where the antimicrobial selects for a gene that confers resistance to more than one antimicrobial class (e.g. *cfr, optrA*) or where co-selection is known for the substance (e.g. co-selection of glycopeptide resistance in enterococci due to use of macrolides) then this should be addressed in the remainder of the risk assessment, including the consequence assessment, taking the prevalence of the gene/co-resistance into account as indicated.

For the hazard identification, consideration should be given to the existence of AMR resistant bacteria and resistance determinants in the EU and globally. The remainder of the risk assessment is performed according to use of the product under EU conditions; although AMR resistant bacteria or resistance determinants identified in third countries and the possibility for their spread into the EU should be addressed. For each hazard identified, the release, exposure and consequence assessments are then mapped forwards individually, for example:

Figure 2: Steps to consider in the AMR risk assessment for each identified hazard



Annex 1 suggests the routes of exposure (food or direct contact) for certain hazards. If it can be justified that one route of exposure is dominant for a specific hazard (e.g. foodborne route for resistant *Salmonella* spp.), then the risk assessment for that hazard may be conducted considering this route alone (section 5).

7.2. Release assessment

This step addresses the biological pathways necessary for use of the specific antimicrobial VMP 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.

Table 2: Release assessment, data requirements and guidance

Data required	Detail	Further guidance on resources and interpretation of data
Product description	Pharmaceutical form	
Conditions of use, estimate of usage	Target species and subcategory (e.g. beef cattle); husbandry practices; disease indication and its prevalence; estimative 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[4], ESVAC data on PCU for the target species[5] 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 should be refined according to the specific conditions. Higher risk would be associated e.g. with common diseases requiring regular treatment, species or husbandry conditions associated with higher antimicrobial usage; husbandry requiring high level of human contact with the target group. Lower risk would be associated with rare diseases etc.
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.	Sales and use data per active substance (and animal (subcategory) species, if available), as collected under Article 57 of the Regulation (ASU database[6]). Animal weights used for the calculation of the denominator are available in the Guideline on the reporting of antimicrobial sales and use in animals at the EU level – denominators and indicators (EMA/CVMP, 2023). Higher risk would be associated with herd/flock treatments, especially those

[4] Eurostat is the statistical office of the European Union. Please see https://ec.europa.eu/eurostat
[5] PCU: Population Correction Unit, as used by ESVAC. Please see https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac 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.
[6] Not available yet

Data required	Detail	Further guidance on resources and interpretation of data
		administered orally via feed 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. Refer to the AMEG's assessment of the impact of the routes of administration on AMR (EMA/CVMP/CHMP, 2019a). Longer duration of treatment effect could be associated with higher risk of AMR selection.
PK and PD of the antimicrobial.	ADME in the target species. Pharmacodynamics - impact on zoonotic and commensal bacteria. Concentration-, time- or co-dependent effects, PAE, Minimal Selective Concentration and sub-MIC effects etc. PK/PD 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' (EMA/CVMP, 2016). See VICH GL 27, section 1.(EMEA/CVMP, 2004).

Data required	Detail	Further guidance on resources and interpretation of data
Occurrence and rate of transfer of resistance determinants.	Studies may be included to demonstrate pre-existence of resistance genes (e.g. metagenomic studies), and *in vitro* rate and extent of resistance selection e.g. *in vitro* mutation frequency studies. If necessary or already available, studies conducted in laboratory animals or the target species can be provided. Note if resistance determinants can be transferred horizontally between bacteria and to bacteria of different species (transformation, transduction, conjugation) and at what rate, and if findings from *in vitro* conditions reflect field situation.	See VICH GL 27, sections 1.5 and 2.1(EMEA/CVMP, 2004). See information on Table 3 of the AMEG's Categorisation of antibiotics in the EU (EMA/CVMP/CHMP, 2019a) and the outcome of Criterion B evaluation for antibiotics, included in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in its most recent version (EMA/CVMP, 2022)[7].
Estimation of the concentration of the antimicrobial agent in the intestinal lumen of the target species 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. (EMEA/CVMP, 2004). 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.
Prevalence of carriage of zoonotic and commensal bacteria in target species 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 and commensal bacteria identified as potential hazards in the target species. In relation to direct contact, literature studies may be available on meat and skin carriage of relevant bacteria in	E.g. EFSA/ECDC European Union One Health Zoonoses Reports (EFSA/ECDC, 2023). 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%.

[7] Criterion B as established in the Annex of Commission Delegated Regulation (EU) 2021/1760.

Data required	Detail	Further guidance on resources and interpretation of data
	the target species and prevalence in the immediate farm environment.	The EU Summary Reports on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union (EFSA/ECDC, 2024). Other sources may also be used, e.g. CEESA[8]. 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%. National reports may also be available from competent authorities in Member States.
Other relevant information.	Studies to investigate the rate of resistance selection in foodborne bacteria following use of the antimicrobial VMP 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.

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

For each hazard, the applicant should provide a discussion that leads to the overall conclusion on the estimated probability (H, M, L, VL) that antimicrobial-resistant bacteria/determinants will be selected for and "released" as a result of the proposed use of the product in target species, 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 treated animal to the point of food consumption or direct contact, and an estimation of the amount of exposure and probability of its occurring.

[8] The Executive Animal Health Study Center (CEESA) collects and aggregates raw industry sales data. Facts and figures available at AnimalhealthEurope webpage. Please see https://animalhealtheurope.eu/facts-and-figures/

The division of the risk assessment into "release" and "exposure" components effectively separates animal and animal treatment elements that are associated with use of the specific VMP (release) from food-chain and human-related elements (exposure). It is acknowledged that certain elements 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 elements are assumed to be independent of the conditions of use of a specific antimicrobial VMP. In order to simplify the approach, the elements 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 species, e.g. meat (beef, pork, chicken, turkey, etc); dairy produce; fish; eggs; honey.	EFSA Comprehensive European Food Consumption Database (EFSA, 2024c), Eurostat, OECD-FAO Agricultural Outlook data (OECD/FAO, 2021). 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 Very 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).	Data should be reported according to the relevant major food categories and animal species e.g. broiler meat, pig meat, milk, cheese. Proportion (%) of positive units.	EFSA/ECDC European Union One Health Zoonoses Reports (EFSA/ECDC, 2023) and baseline survey reports. National Reference Laboratories. 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		
d) Prevalence of resistance to antimicrobial in those bacteria	Information on prevalence of resistance in isolates from carcases at abattoir for relevant animal species and in major food categories at	The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans,

Data required	Detail	Further guidance on resources
	point of sale (where available).	animals and food (EFSA/ECDC, 2024).
e) Data from source attribution studies	Please refer to Scientific Opinion of the Panel on Biological Hazards (EFSA)Overview of methods for source attribution for human illness from foodborne microbiological hazards. (EFSA, 2008).	As published in peer-reviewed scientific journals and official reports. Information may also be available from the outcome of Criterion B evaluation for antibiotics, included in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in its most recent version (EMA/CVMP, 2022)[9].
f) Data to characterise extent of human exposure through direct contact	E.g. number of people exposed to the animal during rearing, carcase at slaughter and food 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. Additionally, information may also be available as the outcome of Criterion B evaluation for antibiotics included on in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in its most recent version (EMA/CVMP, 2022)[9].

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 estimated probability of it 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).

[9] Criterion B as established in the Annex of Commission Delegated Regulation (EU) 2021/1760.[10] Criterion B as established in the Annex of Commission Delegated Regulation (EU) 2021/1760.

7.4. Consequence assessment

This step addresses the potential consequences (adverse health effects on individual patients and burden on healthcare services) of exposure of humans to each of the hazard(s) in the EU and the severity and estimated probability of the consequences to human health. Owing to the need for stringent risk management measures for human last resort antimicrobials, the consequence assessment may be seen as the most important part of this risk assessment process in the context of consideration of new applications for veterinary antimicrobials.

The consequence assessment for resistant bacteria may be informed by that for non-resistant organisms; it relates to the additional burden of disease compared to that caused by a non-resistant strain of a pathogen for which antimicrobial treatment in humans 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 commensal bacteria.

Consideration should be given to patients in both the community and hospitals, with attention to specific vulnerable sub-populations or geographical regions as needed.

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 (or lack of) of alternative antimicrobial treatments for important human indications. Extent of use in human medicine, particularly to treat infections where there are limited alternative treatment options.	See information in the AMEG's Categorisation of antibiotics in the EU (EMA/CVMP/CHMP, 2019a). WHO's Medically Important Antimicrobials List for Human Medicine (WHO, 2024) and AWaRe List (WHO, 2023). 'Advice on the designation of antimicrobials reserved for the treatment of certain infections in humans' (EMA/CVMP, 2022). ESAC database (ECDC, 2024).
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.	
c) Consequences of AMR in human infections.	Number of cases of human infection reported (and estimate of unreported cases) per annum.	EFSA/ECDC European Union One Health Zoonoses Reports (EFSA/ECDC, 2023).

Data required	Detail	Further guidance on resources
	Number/proportion of cases attributed to animal food produce/animal contact. Burden of disease (Cassini et al., 2019): deaths, long term impacts, number of days illness, hospitalisation (length of stay, additional testing and treatment). Prevalence of antimicrobial resistance in human isolates and attribution to animal source (where possible). 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.	ECDC European Surveillance System database (TESSy). Scientific Opinions from EFSA Panel on biological hazards (BIOHAZ) (EFSA, 2024a). Studies on attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area (e.g. Cassini et al. (2019). Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020 (ECDC, 2022).

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

The following categorisation of consequence to human health may be used:

Very low – Resistance to the antimicrobial substance is of low consequence to human health in terms of the frequency of use in humans and that it is used to treat disease(s) in humans for which alternatives are commonly available, i.e., consequences due to resistant organisms are not different to that of susceptible organisms.

Low – Resistance to the antimicrobial substance is of low to medium consequence to human health in terms of the frequency of use to treat disease(s) in humans for which resistant organisms impact on individual patients.

Medium – Resistance to the antimicrobial substance is of medium to high consequence in terms of the frequency of use to treat disease(s) in humans for which resistant organisms impact more seriously on individual patients (e.g. burden of the disease, possibly requiring prolonged hospitalisation).

High – Resistance to the antimicrobial substance is of high consequence to human health because it is a last resort treatment or one of few alternatives for disease(s) in humans and the treatment failure is very severe for individual patients and requires lengthy hospitalisation or results in disability or death.

In order to perform the consequence assessment, the data requested in table 4 should be provided. However, where significant data gaps can be robustly justified for making a thorough consequence assessment, the following CVMP ranking of resistance to antibiotic classes, which was decided on using a **pragmatic approach** to an overall consequence assessment may be used in the risk assessment as described in Chapter 8.

Rankings have been assigned to antibiotic classes based on the outcome of Criterion A evaluation for antibiotics included on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022)[10]. Additionally, discriminatory principles related to their authorisation status for human and veterinary medicine in the European Union were also considered. See Annex 2 for further information.

This leads to the following categorisations:

Table 5: CVMP Ranking of consequence to human health from resistance to specified antibiotic classes after applying a pragmatic consequence assessment

CVMP pragmatic consequence ranking	**Resistance to antibiotic class**
Very Low	Other Quinolones, Amphenicols, Narrow-spectrum penicillins, Sulfonamides, Trimethoprim and derivates, Cyclic polypeptides, Amdinopenicillins, Steroid antibiotics (fusidate), Aminocyclitols (spectinomycin), Orthosomycins, Thiopeptides, Phosphoglycoplipids, Aminocoumarins
Low	Tetracyclines, Pleuromutilins, Ketolides
Medium	Aminopenicillins (with and without beta-lactamase inhibitors), Pseudomonic acids, Nitroimidazoles, Riminofenazines, Sulfones, 1st- and 2nd-generation Cephalosporins, Anti-staphylococcal penicillins, Sulfonamides and trimethoprim, Streptogramins, Lincosamides
High	3rd- and 4th-generation Cephalosporins, Polymyxins, Fluoroquinolones, Rifamycins, Aminoglycosides, Macrolides, Drugs solely to treat tuberculosis

Note that certain antibiotic classes that are of last resort in human medicine and that are not authorised in veterinary medicine in the EU have not been included in this table as they are in the list of antimicrobials reserved for human treatment only in accordance with Article 37(5) of the Regulation and listed in the Annex to Commission Implementing Regulation (EU) 2022/1255. Furthermore, owing to changes in resistance trends and patterns of antibiotic use, the importance of different classes may

[10] Criterion B as established in the Annex of Commission Delegated Regulation (EU) 2021/1760.

change over time. In addition, important novel molecules may be developed within a class to overcome specific resistance mechanisms. For these reasons, some deviation from the table may be necessary. This table will be updated periodically.

8. Overall qualitative risk estimation

The risk estimation integrates the results from the release, exposure and consequence assessments (including if using CVMP pragmatic consequence category of resistance to different antibiotic groups) to produce an estimate of the risk to public health from antimicrobial-resistant bacteria resulting from the use of the proposed VMP 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, with a separate risk estimate being made for each hazard. Each risk estimate 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. food-animal production systems, geographical regions) should also be briefly addressed where relevant.

Risk estimate matrix

Release	Exposure	Consequence	Risk Estimate
VERY LOW	VERY LOW	VERY LOW	VERY LOW
		LOW	VERY LOW
		MEDIUM	VERY LOW
		HIGH	LOW
	LOW	VERY LOW	VERY LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	LOW
	MEDIUM	VERY LOW	VERY LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	LOW
	HIGH	VERY LOW	LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	MEDIUM
LOW	VERY LOW	VERY LOW	VERY LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	LOW
	LOW	VERY LOW	LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	MEDIUM
	MEDIUM	VERY LOW	LOW
		LOW	LOW
		MEDIUM	MEDIUM
		HIGH	MEDIUM
	HIGH	VERY LOW	LOW
		LOW	MEDIUM
		MEDIUM	MEDIUM
		HIGH	HIGH
	VERY LOW	VERY LOW	VERY LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	LOW
	LOW	VERY LOW	LOW
		LOW	LOW

MEDIUM		MEDIUM	MEDIUM
		HIGH	MEDIUM
	MEDIUM	VERY LOW	LOW
		LOW	MEDIUM
		MEDIUM	MEDIUM
		HIGH	HIGH
	HIGH	VERY LOW	LOW
		LOW	MEDIUM
		MEDIUM	HIGH
		HIGH	HIGH
HIGH	VERY LOW	VERY LOW	LOW
		LOW	LOW
		MEDIUM	LOW
		HIGH	MEDIUM
	LOW	VERY LOW	LOW
		LOW	MEDIUM
		MEDIUM	MEDIUM
		HIGH	HIGH
	MEDIUM	VERY LOW	LOW
		LOW	MEDIUM
		MEDIUM	HIGH
		HIGH	HIGH
	HIGH	VERY LOW	MEDIUM
		LOW	HIGH
		MEDIUM	HIGH
		HIGH	HIGH

Definitions

Antibiotic – Defined by the Regulation as 'any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases'.

Antimicrobial – Defined by the Regulation as 'any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals and anti-protozoals'. In the context of this guideline, the focus is on compounds acting against bacteria.

Antimicrobial resistance – Defined by the Regulation as 'the ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species'.

Clinical breakpoint (CBP) – For the purposes of this Guideline, the CBP refers to minimum inhibitory concentrations (MICs) that separate bacterial strains where there is a high likelihood of treatment success at accepted clinical dosage regimens from strains where treatment is more likely to fail (Turnidge & Paterson, 2007).

Co-resistance –For the purposes of this Guideline, "co-resistance" means 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 – For the purposes of this Guideline, "co-selection of resistance" means 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 – For the purposes of this Guideline, "cross-resistance" means a single resistance mechanism that 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).

Epidemiological cut-off value (ECOFF) – For the purposes of this Guideline, "epidemiological cut-off value" refers to the MIC for an antibiotic that distinguishes wild-type populations of a bacterial species from those with acquired or selected resistance mechanisms.

Foodborne commensal bacteria – [VICH GL 27(EMEA/CVMP, 2004)] 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(EMEA/CVMP, 2004)] 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.

Resistance determinant – For the purposes of this Guideline, "resistance determinant" means any gene or gene mutation that confers resistance.

Variability – For the purposes of this Guideline, "variability" means the heterogeneity of the subjects modelled, including both randomness and inter-individual variability. Variability cannot be reduced by additional data or information.

Zoonotic bacteria (FAO/WHO/OIE, 2008) - 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 indicator commensal bacteria present in different food-producing animal species in which carriage of AMR could be a hazard to human health (non-exhaustive):

Bacterial species	**Routes of exposure** Primary route **in bold**	**Animal species that are possible sources**
Zoonotic bacteria		
Campylobacter spp. e.g. *C. jejuni, C. coli*	**Food** (meat, milk/dairy)	**Poultry** (*C. jejuni*) Pigs (*C. coli*, *C. jejuni*) Cattle Sheep, goats Fish
Salmonella spp.	**Food** (meat, eggs, milk/dairy) Contact	**Pigs** (*S. Typhimurium*) **Poultry** (*S. Infantis*, *S. Enteritidis*) Cattle (*S. Typhimurium*, *S. Dublin*) Sheep, goats Horses Fish
Leptospira hardjo	**Contact**	**Cattle**
Coxiella burnetii	**Contact**, local environment. (Food – milk/dairy)	Cattle Sheep, goats
Staphylococcus aureus including LA-MRSA	**Contact** (Food – meat, milk)	Pigs Poultry Cattle Horses
Brucella spp.	**Contact** Food (milk/dairy)	Cattle (*B. abortus*) Sheep, goats (*B. melitensis*) (Pigs) (*B. suis*)
Bacillus anthracis	**Contact**	Cattle, sheep, goats, pigs, horses
Chlamydophila spp.	**Contact**	Sheep (*C. abortus*) Poultry (*C. psittaci*)

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.
Clostridioides difficile Role as zoonotic bacteria under investigation (Knight & Riley, 2019; Rodriguez et al., 2016; Spigaglia et al., 2015; Weese, 2020)	**Food** (meat)	Pigs Cattle
Indicator commensal bacteria		
E. coli	**Food** Contact	All
Enterococcus faecalis, faecium	**Food** Contact	All
Aeromonas hydrophila	Food, contact	Fish

Annex 2

Pragmatic consequence assessment

For the pragmatic consequence assessment, account has been taken of the outcome of the evaluation of Criterion A (criterion of high importance to human health), as established in the Annex of Commission Delegated Regulation (EU) 2021/1760, per each antibiotic class in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022).

Criterion A is considered fulfilled if a substance is **(a)** sole or last resort, or **(b)** an essential component of limited treatment alternatives, for serious or life-threatening infections in humans (see Regulation (EU) 2021/1760 for detail of the sub-criteria). Further evaluations were based on text of the supporting HRL evaluation tables together with the following additional discriminatory principles:

• Classes meeting criterion A in the HRL were all assigned to PCA ranking **not less** than **medium** (i.e., high or medium).

• Classes **not** meeting criterion A in the HRL and that are approved for human medicine in the EU were all assigned to PCA ranking **not higher** than **medium** (i.e., medium, low or very low).

• Classes **not** meeting criterion A in the HRL and that are not approved for human and veterinary medicine in the EU were assigned to PCA ranking **not higher** than **low** (i.e., low or very low).

Some antibiotic classes were assigned the ranking 'low' or 'very low', although they are approved for human and veterinary medicine in the EU, as several alternatives are available in the human therapeutical arsenal.

Pragmatic consequence ranking (H/M/L/VL) of the consequences to human health resulting from resistance to antibiotic classes, excluding those on the Human Reserved List (HRL)[(1)]

AM class	**HRL Criterion A[(2)] met** yes/no	**Pragmatic consequence ranking**	**Notes** The information below is based on the outcome of Criterion A[(2)] evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
Rifamycins	yes	H	Rifamycins fulfilled criterion A as limited treatment alternatives available for management of serious, life-threatening infections in humans such as mycobacterial infections.
3rd- and 4th-generation cephalosporins	yes	H	3rd- and 4th-generation cephalosporins fulfilled criterion A as limited treatment alternatives available for a high number of

AM class	HRL Criterion A(2) met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A(2) evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
			patients with various serious, life-threatening infections.
Polymyxins	yes	H	Polymyxins fulfilled criterion A as one of limited treatment alternatives for serious, life-threatening healthcare-associated infections due to carbapenem-resistant Enterobacterales, MDR *Acinetobacter baumannii* and MDR *Pseudomonas aeruginosa.*
Fluoroquinolones	yes	H	Fluoroquinolones fulfilled criterion A as limited treatment alternatives available for management of various serious, life-threatening infections in humans including those caused by Gram-negative bacilli, respiratory pathogens and TB.
Macrolides	yes	H	Macrolides are among the most used classes of antibiotics. They are used in the management of respiratory tract infections, acute bacterial sinusitis, acute bacterial otitis media, pharyngitis, tonsillitis, mild to moderately severe community-acquired pneumonia, uncomplicated chlamydia infections, urethritis, cervicitis, acute exacerbation of chronic bronchitis (adequately diagnosed), skin and soft tissue infections, campylobacteriosis and *H. pylori* infections. Macrolides are an important treatment alternative for patients allergic to penicillin and cephalosporins. Macrolides fulfilled criterion A as one of limited treatment options for these infections.
Aminoglycosides	yes	H	Aminoglycosides fulfilled criterion A as limited treatment alternatives available to treat severe infections such as septicaemia, enterococcal endocarditis, meningitis,

AM class	HRL Criterion A[(2)] met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A[(2)] evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
			complicated UTI and neonatal infections. They are highly important to treat serious infections caused by carbapenem-resistant Gram-negative bacteria.
Drugs used solely to treat tuberculosis (TB)	yes	H	TB drugs fulfilled criterion A based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening mycobacterial infections. The class includes first-line anti TB drugs, and those for multidrug resistant TB.
Nitroimidazoles[(3)]	yes	M	Nitroimidazoles fulfilled criterion A on the basis of their importance to treat a wide range of serious anaerobic infections, particularly post-operative infections due to Bacteroides and anaerobic streptococci; septicaemia, peritonitis, pelvic infections, necrotising pneumonia, osteomyelitis, puerperal sepsis and *Clostridioides difficile* in the paediatric population.
Pseudomonic acids	yes	M	Pseudomonic acids (mupirocin) fulfilled criterion A due to its importance in the patient management approach for serious infections due to MRSA. In the EU, mupirocin is used topically for MSSA and MRSA decolonisation and is essential for management of patients undergoing e.g. cardiothoracic and orthopaedic surgeries or stem-cell transplants in hospitals.
Riminofenazines	yes	M	Clofazimine fulfilled criterion A as one of limited treatment alternatives for management of serious life-threatening infections in humans. It has been granted orphan drug status in the EU for the treatment of non-tuberculous mycobacterial

AM class	HRL Criterion A(2) met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A(2) evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
			lung disease. However, clofazimine is mainly used for leprosy; although this disease is uncommon in the EU.
Sulfones(4)	yes	M	Sulfones fulfilled criterion A as one of limited alternatives for leprosy which is a serious life-threatening infection in humans; however, this disease is uncommon the EU.
1st- and 2nd-generation cephalosporins and cephamycins	yes	M	1st- and 2nd-generation cephalosporins fulfilled criterion A because of their essential role for perioperative prophylaxis in humans. 1st-generation cephalosporins are also used as chemoprophylaxis in preventing group B streptococcal disease in the new-born and cefazolin is a treatment option for MSSA bacteraemia and MSSA endocarditis. 2nd-generation cephalosporins are also first empirical choice for UTI treatment in children. For these indications, there are alternatives but some of them belong to classes that are classified by WHO as Critically Important Antimicrobials.
Anti-staphylococcal penicillins	yes	M	Anti-staphylococcal penicillins fulfilled criterion A being an essential component for treatment of serious life-threatening infections, in particular MSSA bacteraemia and endocarditis. Alternative treatment for invasive staphylococcal infections (i.e., bacteraemia and endocarditis) include 1st-generation cephalosporins but the anti-staphylococcal penicillins are the preferred option. They are also used for skin and soft tissue infections, bone and joint infections, pneumonia and meningitis.

AM class	HRL Criterion A(2) met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A(2) evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
Sulfonamides & trimethoprim	yes	M	Co-trimoxazole fulfilled criterion A being one of limited treatment alternatives, specifically for life-threatening *Pneumocystis jirovecii* pneumonia in immunocompromised patients and nocardiosis in immunosuppressed patients. Co-trimoxazole is further among first choice agents for the treatment of MRSA infections, particularly those being community acquired. Co-trimoxazole is the only available alternative against multidrug *resistant S. maltophilia* and *B. cepacia.*
Aminopenicillins with beta-lactamase inhibitors (BLIs)	yes	M	Aminopenicillin with BLIs are well established in therapy of a wide range of infections. They fulfilled criterion A as essential components of the limited treatment alternatives available for management of serious, life-threatening infections in humans, particularly those due to beta-lactamase-producing strains.
Aminopenicillins without BLIs	no	M	Aminopenicillins did not fulfil criterion A as there are alternatives for all the authorised conditions. They are recommended for a wide range of infections, making ampicillin one of the most prescribed antibiotics in human medicine. Even though an increasing prevalence of beta-lactamase producing organisms has resulted in reduced use of aminopenicillins as monotherapy, they are still used with very high frequency in human medicine and thus are ranked on the same level as aminopenicillins with BLIs.
Streptogramins	no	M	Streptogramins (i.e. pristinamycin and quinupristin-dalfopristin) were previously one of few available treatments for

AM class	HRL Criterion A(2) met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A(2) evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
			vancomycin-resistant (VR) and MDR *E. faecium* and MDR *Staphylococcus aureus* infections in humans but have now been replaced with safer alternatives and have limited availability in the EU/EEA.
Lincosamides	no	M	Lincosamides did not fulfil criterion A as alternatives are available. However, clindamycin plays a very important role in the treatment of infections in humans, including the treatment of invasive disease due to *Streptococcus* beta-haemolytic group A, staphylococcal infections (including those caused by community-acquired MRSA), and anaerobic infections. Clindamycin is also regarded as a first-choice medicine for bacterial vaginosis.
Ketolides	no	L	Ketolides were developed for treatment of community-acquired pneumonia, especially those infections resistant to beta-lactams and macrolides; however, they have been withdrawn from the EU market due to safety concerns. It was noted that if authorised in the EU, ketolides would not fulfil criterion A due to limited usefulness in the EU/EEA and other existing treatment alternatives.
Tetracyclines	no	L	In the EU, tetracyclines were not considered to meet criterion A as newer treatment alternatives are available. They are authorised for a wide range of indications and may also be used to treat atypical pathogens e.g. *Rickettsia* spp., *Chlamydia* spp., and *Mycoplasma pneumoniae*.
Pleuromutilins	no	L	Lefamulin is approved in human medicine for the treatment of community-acquired pneumonia (CAP) in adults when it is

AM class	HRL Criterion A(2) met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A(2) evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
			considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP or when these have failed. However, pleuromutilins did not fulfil criterion A due to the availability of alternatives to treat this infection in the EU.
Other quinolones	no	VL	Other quinolones (e.g. nalidixic acid) have been used historically in human medicine to treat uncomplicated UTI; however, in the EU it was recommended that marketing authorisations of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid to be suspended due to safety concerns Other quinolones did not meet criterion A as alternatives are available.
Sulfonamides	no	VL	Sulfonamides did not fulfil criterion A, as there are treatment alternatives. Clinical use is decreasing due to resistance.
Trimethoprim and derivatives	no	VL	TMP did not fulfil criterion A, as there are treatment alternatives. Clinical use is decreasing due to resistance.
Amdinopenicillins	no	VL	Amdinopenicllins are mainly used to treat uncomplicated UTI due to Enterobacterales infections. They did not fulfil criterion A as sufficient alternatives are available.
Amphenicols(5)	no	VL	Amphenicols (chloramphenicol) did not fulfil criterion A due to limited use in human medicine in the EU and due to the existence of safer treatment alternatives. Chloramphenicol is no longer an antibiotic of first choice due to serious adverse effects.

AM class	HRL Criterion A(2) met yes/no	Pragmatic consequence ranking	Notes The information below is based on the outcome of Criterion A(2) evaluation for antibiotics which can be found on Tables 7 to 61 in the Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans (EMA/CVMP, 2022). Please refer to this advice for further information, including references.
Narrow-spectrum penicillins	no	VL	Narrow-spectrum penicillins are authorised for a wide range of indications, but their clinical usefulness is limited by the prevalence of resistance. Narrow-spectrum penicillins did not fulfil criterion A as alternatives are available.
Steroid antibacterials (fusidate)	no	VL	Fusidic acid is mainly used for the topical treatment of staphylococcal skin and eye infections as well as an alternative to mupirocin for MSSA and MRSA decolonisation. Steroid antibiotics did not fulfil criterion A as alternatives are available.
Aminocyclitols (spectinomycin)	no	VL	Spectinomycin has limited availability in the EU for treatment of uncomplicated gonorrhoea. Aminocyclitols did not fulfil criterion A due to limited use in the EU/EEA and availability of alternatives.
Cyclic polypeptides	no	VL	Bacitracin is mostly used in combination with other antimicrobials for topical treatment of various dermatoses. Cyclic polypeptide antibiotics did not fulfil criterion A due to the limited use in human medicine and other treatment alternatives.
Orthosomycins, Thiopeptides, Phosphoglycoplipids	no	VL	These classes are not currently authorised for use in human medicines in the EU. They did not fulfil criterion A as no evidence could be found to confirm their importance of use in human medicine.
Aminocoumarins	no	VL	Novobiocin was previously used for treatment of staphylococcal infections but is not currently authorised in the EU; aminocoumarins did not fulfil criterion A as alternatives are available.

(1) To be included on the HRL, substances had to meet three criteria: A – essential need for humans, B - relating to risk of AMR transfer, and C - lack of essential need for animals. Substances that met all 3 of the HRL criteria have not been included in this table as they are prohibited for use in animals.
(2) Criterion A as established in the Annex of Commission Delegated Regulation (EU) 2021/1760. Criterion A is considered fulfilled if a substance is of high importance of the antimicrobial to human health to treat serious, life-threatening infections that have no or limited availability of alternative treatments.
(3) Metronidazole, dimetronidazole, ronidazole;
(4) Dapsone;
(5) Chloramphenicol: are prohibited for use in food-producing animal species (see table 2 of Commission Regulation (EU) No 37/2010) (Official Journal of the European Union, 2009).

Acronyms

ADME	Absorption, Distribution, Metabolism and Excretion
AM	Antimicrobial
AMEG	Antimicrobial Advice Ad hoc Expert Group: Established jointly under CVMP and CHMP to provide guidance on the impact on public health and animal health of the use of antibiotics in animals, and on the measures to manage the possible risk to humans.
AMR	Antimicrobial resistance
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARG	Antimicrobial resistance gene
CEESA	The Executive Animal Health Study Centre (CEESA): European Antimicrobial Susceptibility Surveillance in Animals Programme (EASSA).
CVMP	Committee for Medicinal Products for Human Use
CIA	Critically Important Antimicrobial
CVMP	Committee for Medicinal Products for Veterinary Use
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption. EMA's ESVAC project collected data from European countries on the sales and use of antimicrobial medicines in animals from 2009 to 2023
EURL-AR	EU Reference Laboratory – Antimicrobial Resistance: Body providing scientific advice to the Commission in relation to monitoring schemes for AMR.
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice (VICH GL 9)
GLP	Good Laboratory Practice
HMA	Heads of Medicines Agencies: Network of the heads of National Competent Authorities responsible for the regulation of human and veterinary medicinal products in the EEA.
MIC	Minimal inhibitory concentration
WOAH	World Organisation for Animal Health (founded as OIE)
PAE	Post antibiotic effect
PK/PD	Pharmacokinetic-pharmacodynamic

RONAFA	EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety
SPC	Summary of Product Characteristics
VetCAST	Veterinary sub-committee of European Committee on Antimicrobial Susceptibility Testing
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary Medicinal Product