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

Draft

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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 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 2011-2015¹ 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 27² 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 for antimicrobial veterinary medicinal products for use in food producing species. The consequences of AMR that may be considered include loss of treatment options, human illness (morbidity), hospitalisation and death (mortality).

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

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

The scope of this guidance extends to:

- Veterinary Medicinal Products (VMPs) intended to treat food producing species, and
- Antimicrobial VMPs that potentially select resistant bacteria and that may be transmitted through foodstuff of animal origin or by direct contact with the target species and 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. 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 recently published a reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP/401740/2013).

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.
- 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.:

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EMA/CVMP/AWP/706442/2013
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.

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 13.2 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 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, 2001⁴; 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 77-2011⁵) and the requirements in place in other jurisdictions (FDA⁶, Health Canada⁷, APVMA⁸). 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 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 public 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 development 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.

- **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 a 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.

It is recognised that there are likely to be substantial data gaps that preclude a quantitative approach to this risk assessment. Likewise, given the current level of knowledge and data available, semi-quantitative categorisation of the factors on the risk pathway and subsequently the steps in the risk assessment might be arbitrary. Therefore use of a risk matrix based on the categorisation of the individual steps is not proposed as they cannot be logically combined to determine an overall effect. 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. The applicant should comment on any assumptions that have been made, especially in relation to data gaps or poor understanding of risk pathways. The uncertainty and variability associated with each factor/parameter and the influence this may have on the reliability 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.

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

**Hazard Identification** — Identification of resistant bacteria/determinants that are selected by use of the antibiotic in target animal species and may be associated with human illness.

**Release Assessment** — Pathways and probability that resistant bacteria are present in the animal as a result of use of the VMP at the time of “release” (slaughter, collection of food produce or via direct animal contact).

**Conditions of use of antimicrobial VMP in target animal**

**Selection and dissemination of AMR in and between animals**

**Prevalence of AMR in target animal at point of harvest/slaughter**

**Prevalence of AMR in target animals available to be transmitted via direct contact**

**Prevalence of contamination of unprocessed food with AMR bacteria**

**Food processing, preparation, storage, etc + microbial factors affecting frequency and concentration of bacteria in food**

**Level of food consumption, Prevalence + bacterial load in food at consumption, Prevalence of AMR in contaminating bacteria**

**Probability and extent of human exposure to AMR through direct contact**

**Consequence Assessment** — The probability and severity of adverse human health effects following exposure to resistant bacteria/determinants originating from treated animals and colonization and infection of human.

**Risk Estimation** — Integration of (hazard), release, exposure and consequence assessments.

**Exposure Assessment** — Pathways necessary for exposure of humans to resistant bacteria/determinants originating from treated animal to the point of food consumption or direct contact and an estimation of the probability of its occurring.
6. Data sources and quality

Possible sources of information include, for example, data included 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.

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 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 mobile-mediated resistance determinants to other bacteria that are pathogenic in humans. 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.

Table 1: Hazard identification, data requirements and guidance.

<table>
<thead>
<tr>
<th>Data required</th>
<th>Detail</th>
<th>Further guidance on resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance-specific information.</td>
<td>Antimicrobial class.</td>
<td>See VICH GL 27, section 1.1</td>
</tr>
<tr>
<td></td>
<td>Mechanism of action.</td>
<td>See VICH GL 27, section 1.2</td>
</tr>
<tr>
<td></td>
<td>Spectrum of activity.</td>
<td>See VICH GL 27, section 1.3</td>
</tr>
<tr>
<td>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.</td>
<td>This includes:</td>
<td>See VICH GL27, section 1.3. In addition consider bacteria that may be transmitted by direct contact.</td>
</tr>
<tr>
<td></td>
<td>• Foodborne pathogens (e.g. Campylobacter, Salmonella);</td>
<td></td>
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<tr>
<td></td>
<td>• Bacteria that could be transmitted by direct contact (e.g. Staphylococcus aureus);</td>
<td></td>
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<tr>
<td></td>
<td>• Indicator/commensal bacteria that may carry</td>
<td></td>
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<tr>
<td>Data required</td>
<td>Detail</td>
<td>Further guidance on resources</td>
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<tr>
<td>Mobile resistance determinants that could be passed to human pathogenic bacteria (e.g. <em>Escherichia coli</em>, <em>Enterococcus</em> spp.).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known resistance determinants or mechanisms associated with the antimicrobial in animal and human bacteria.</td>
<td>E.g. antimicrobial inactivation, alteration of target, efflux pumps. Location of resistance determinants, e.g. chromosomal, plasmid, transposons.</td>
<td>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.</td>
</tr>
<tr>
<td>Occurrence of cross-resistance and co-resistance.</td>
<td>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.</td>
<td>See VICH GL 27, sections 1.6 and 1.7 Cross-reference can be made, as appropriate to the information supplied in accordance with the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (currently under revision).</td>
</tr>
<tr>
<td>Susceptibility data (MIC distribution /MBC) for the bacteria of human health concern.</td>
<td>MIC values should be determined with validated methods, where possible. Clinical and microbiological breakpoints (ECOFFs) should be considered in the assessment.</td>
<td>See VICH GL 27, section 1.3</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Data required</th>
<th>Detail</th>
<th>Further guidance on resources and interpretation of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product description</td>
<td>Formulation</td>
<td></td>
</tr>
<tr>
<td>Conditions of use</td>
<td>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.</td>
<td>Eurostat(^9), ESVAC(^{10}) data on PCU(^{11}). Higher risk would be associated e.g. with common diseases requiring regular treatment, major species; husbandry requiring high level of human contact with the target group. Lower risk would be associated with minor species, rare diseases.</td>
</tr>
<tr>
<td>Resistance selection pressure</td>
<td>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.</td>
<td>ESVAC sales data. Higher risk would be associated with herd/flock treatments, especially those administered orally via food or drinking water. Lower risk would be associated with individual animal treatments, and with products which are administered locally so that gastrointestinal-tract exposure is limited. Longer duration of treatment effect could be associated with higher risk of AMR selection.</td>
</tr>
<tr>
<td>PK/PD of the antimicrobial</td>
<td>ADME(^{12}) in the target animal species. PD: concentration- or time-dependent effects, PAE(^{13}), sub-MIC(^{14}) effects etc. PK/PD(^{15}) in respect of bacterial species identified as potential hazards to human health.</td>
<td>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).</td>
</tr>
</tbody>
</table>

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\(^9\) Eurostat is the statistical office of the European Union. 

\(^{10}\) The European Surveillance of Antimicrobial Consumption. 


\(^{12}\) ADME: absorption, distribution, metabolism, excretion.

\(^{13}\) PAE: post antibiotic effect

\(^{14}\) MIC: minimal inhibitory concentration

\(^{15}\) PK/PD: pharmacokinetics/pharmacodynamics
<table>
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<tr>
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<tbody>
<tr>
<td>Occurrence and rate of transfer of resistance determinants</td>
<td>Studies may be included to demonstrate both <em>in vitro</em> or <em>in vivo</em> rate and extent of resistance development. This may include studies conducted in laboratory animals or the target species, and <em>in vitro</em> 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 <em>in vitro</em> conditions reflect field situation?</td>
<td>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)(^\text{16}).</td>
</tr>
<tr>
<td>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.</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Prevalence of carriage of zoonotic bacteria and commensals in target animal population and baseline prevalence of resistance in those bacteria.</td>
<td>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 skin carriage of relevant bacteria in the target species and prevalence in the immediate farm</td>
<td>E.g. The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-Borne Outbreaks (EFSA/ECDC).(^\text{17}) The European Union Summary Report on Antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union (EFSA/ECDC)(^\text{18}) Other sources may also be used, e.g. CEESA.(^\text{19})</td>
</tr>
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\(^{19}\) The European Animal Health Study Centre (CEESA): European Antimicrobial Susceptibility Surveillance in Animals Programme (EASSA).
Other relevant information

<table>
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<th>Data required</th>
<th>Detail</th>
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<tr>
<td>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.</td>
<td>Influence of withdrawal period or period between treatment and slaughter could be considered in the assessment.</td>
<td></td>
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</tbody>
</table>

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

### 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.

<table>
<thead>
<tr>
<th>Data required</th>
<th>Detail</th>
<th>Further guidance on resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Human consumption patterns for food produce from target species in the EU</td>
<td>This refers to major produce classes associated with the target animal, e.g. meat (beef, pork, chicken, turkey, etc); dairy produce; fish; eggs</td>
<td>EFSA EU Comprehensive Food Consumption Database&lt;sup&gt;20&lt;/sup&gt;/Eurostat</td>
</tr>
<tr>
<td>b) Prevalence of food contamination at point of consumption with relevant bacteria</td>
<td></td>
<td>EFSA/ECDC Zoonosis reports</td>
</tr>
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<tbody>
<tr>
<td>c) Microbial load of food at point of consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Prevalence of resistance to antimicrobial in those bacteria</td>
<td></td>
<td>The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food</td>
</tr>
<tr>
<td>e) Data from source attribution studies</td>
<td>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. <em>The EFSA Journal</em> (2008) 764,1-43(^{21})</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>A distinction between professional contact (occupational hazard reports) and occasional contact (e.g. children on farm visits) might be indicated</td>
<td></td>
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</tbody>
</table>

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.

7.4. **Consequence assessment**

This step addresses the potential consequences (adverse health effects) of exposure of humans to the hazard(s) 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.

Table 4: Consequence assessment, data requirements and guidance.

<table>
<thead>
<tr>
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<th>Further guidance on resources</th>
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</thead>
<tbody>
<tr>
<td>a) Relative importance of the antimicrobial to human medicine</td>
<td>Spectrum of activity and indications for use in humans. Availability of alternative antimicrobial treatments. Extent of use in human medicine.</td>
<td>See information in response to Q.2 of the Commission’s request for scientific advice on the impact on public and animal health of the use of antibiotics in animals (Table 2). ESAC database(^\text{22}).</td>
</tr>
<tr>
<td>b) Dose-response relationships (where available)</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>c) Consequences of AMR in human infections</td>
<td>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). Any increase in transmission or severity and duration of illness due to increased</td>
<td>The European Union Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents and Food-borne Outbreaks. European Surveillance System (TESSy)(^\text{23}) – ECDC. Scientific Opinions from EFSA Panel on biological hazards (BIOHAZ).</td>
</tr>
</tbody>
</table>


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.

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 the hazard identified to the unwanted outcome. 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) should also be briefly addressed. As terms such as high, medium and low are subjective, these should be explained where used.

Definitions

**Adverse health effect** - An unwanted outcome in humans. Specifically here, this is a human illness due to AMR organisms and determinants 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 and mortality.

**Antimicrobial** - For this guidance, an “antimicrobial” is defined as an active substance of synthetic or natural origin which destroys microorganisms, suppresses their growth or their ability to reproduce in animals or humans. In this context, antivirals, antiparasitics and disinfectants are excluded from the definition.
**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). Microbiological resistance against an antimicrobial is considered to be present if the Minimum Inhibitory Concentration (MIC) exceeds the epidemiological cut-off value.

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

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

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

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

**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 antibiotic resistance, the hazards are antibiotic-resistant micro-organisms or their transferable genetic determinants.

**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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References


EFSA (European Food Safety Authority), 2008. Scientific Opinion of the Panel on Biological Hazards on fooodborne antimicrobial resistance as a biological hazard. EFSA Journal. 765, 1-87.


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