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# 5 Answer to the request from the European Commission for 6 updating the scientific advice on the impact on public 7 health and animal health of the use of antibiotics in 8 animals - Preliminary risk profiling for new antimicrobials

9 Draft

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|---|---|
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# Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Preliminary risk profiling for new antimicrobials

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# 1. Summary

As part of its scientific advice to the European Commission (EMA/AMEG, 2014), the Antimicrobial Advice ad hoc Expert Group (AMEG) was asked to consider the possible impact that authorisation of new classes of antibiotics for use in animals could have on the treatment of antibiotic-resistant infections in humans. The advice concluded that a specific risk assessment would be needed for each new substance/class to assess the importance of the substance to human health and the risk of AMR transfer from treated animals to humans. Further to this conclusion, it was recommended that a hazard characterization for new antimicrobials, performed prior to the submission of a marketing authorization application, could be used to give an early indication to future marketing authorisation (MA) applicants of the need for risk management measures to be applied to associated veterinary medicines. The 'early hazard characterization' could also be used to assess if restrictions should be applied to use of new molecules under the prescribing cascade[1].

In a new mandate received by the EMA in 2017, the Commission requests to further elaborate on the proposed early hazard characterization. In addition to the outcomes noted above, as mentioned in the background to the mandate, the methodology might be used in the preparation of a list of antimicrobial substances to be reserved for treatment of human infections only.

Specifically, the EMA has been requested to provide:

- 'Detailed analysis of the benefits and risks of an early hazard characterisation: if the analysis would merit continuing with the proposal:
  - Further details on the procedure of the early hazard characterisation,
  - Technical requirements of the early hazard characterisation'

In order to avoid confusion with terminology used by other organisations, the AMEG has chosen to use the term 'preliminary risk profile' (PRP) in place of 'early hazard characterization'.

The use of the PRP to inform the development of antimicrobial veterinary medicinal products (VMPs) is addressed first (chapter 3). In this case, the purpose of the PRP is to consider the AMR risk to public health from the new substance or VMP and the potential need for risk management measures to be applied. The intended benefit is to provide increased regulatory predictability at an early stage of product development and thereby encourage the pharmaceutical industry to develop new antimicrobials for animals, or to further develop existing antimicrobial VMPs. It is suggested that the PRP may be undertaken within the current procedure for provision of scientific advice from the Committee for Medicinal Products for Veterinary Use (CVMP); this would take into account stakeholders' comments regarding the need to have an efficient procedure with clear timelines, and would ensure confidentiality. Provision could be made for consultation with CVMP working groups (AMEG, Antimicrobials Working Party - AWP) to promote a One Health approach. The identified supporting data required and methodology are based on an abridged version of the CVMP's draft guideline on the assessment of the risk to public health from antimicrobial VMPs (EMA/CVMP/AWP, 2015), with the level of assessment and advice that can be offered dependent on the extent of data provided by the applicant (which may be information on substance only, or in addition target animal species and pharmaceutical form). The profiling includes the conventional steps in risk assessment: hazard identification leading to release, exposure and consequence assessments, and their integration

[1] Articles 10 and 11 of Directive 2001/82/EC. The prescribing cascade is a provision in legislation which, when no suitable authorised product is available and under exceptional circumstances, allows a veterinarian to use a veterinary medicinal product outside of its authorised conditions of use, or to use an unauthorised medicine, according to given criteria.

into a high level estimate of the AMR risk to human health. Certain of the key risk indicators used are criteria considered for the AMEG's categorization of antimicrobials which will therefore be influential. In addition, the consequence to animal health and the livestock industry of any restriction on use of the antimicrobial medicine in animals is also taken into consideration ('risk-risk' scenario). An outcome of the PRP is the identification and evaluation of potential AMR concerns for human health due to use of the antimicrobial substance or medicine. During the process any data gaps which should be addressed in a subsequent MA application can be identified. Finally, at a high level, options can be proposed for specific risk management measures, if needed.

Amongst the provisions in the new Regulation on veterinary medicinal products (Official Journal of the European Union, 2019) are proposals to reserve certain critically important antimicrobials (CIAs) for use in humans only, and to restrict or place conditions around the off-label use of other CIAs. In this regard, an adapted PRP could provide a transparent and evidence-based tool to assist decision-making, and help to achieve a balance between the need to protect public and animal health from AMR versus the risk to animal health and welfare and agriculture due to lack of availability of antimicrobial treatments. The adapted PRP is addressed in chapter 4. For this purpose, the data requirements are expanded to include consideration of the importance of the substance to animal health and any particular risks to animal health from AMR in animal pathogens that may result from cascade use. The methodology for the risk profiling follows that described above. In addition to the risk estimation, attention is also given to the 'risk-risk' scenario by considering information on the potential benefits resulting from use of the antimicrobial under the cascade to treat specific diseases, the availability of alternative treatments for these conditions and any impact on animal health and welfare, aquaculture and farming if the condition cannot be treated.

# 2. Introduction

## *2.1. Background*

### 2.1.1. AMEG opinion requested in 2013

The European Commission (EC) requested in April 2013 scientific advice from the European Medicines Agency (EMA) on the impact of the use of antibiotics in animals on public health and animal health and measures to manage the possible risk to humans. The scientific advice was prepared by the Antimicrobial Advice Ad Hoc Expert Group (AMEG) and the response was published by the EMA in December 2014 (EMA/AMEG, 2014).

Part of this advice was to consider the impact on AMR of the authorisation of new classes of veterinary antimicrobials, and if there is a need to restrict or ban the use in animals of certain new classes that are currently not authorised.

The advice concluded that a specific risk assessment would be needed for each new antimicrobial substance/class, to assess its importance to human health and the risk of transfer of resistance from treated animals to humans. In addition, it was recognised that in order to obtain a marketing authorisation for a new VMP containing such a substance, this risk assessment would be tailored to the conditions of use of the product (e.g. target species, indications) and form part of an overall benefit-risk assessment that would also take into account the treatment benefit of the product for animal health.

Further to this conclusion, it was however noted that a substance-related assessment could be of value:

1. To indicate if an antimicrobial substance should be restricted or banned from use in food-producing animals under the Cascade.
2. To provide an indication to potential applicants for marketing authorisations for new antimicrobial VMPs (for food-producing species) as to the potential AMR risks to public health and the need for risk management measures.

The advice also concluded that authorisation of completely new classes of antimicrobials for use in animals could decrease the animal and public health risk due to AMR provided that co-selection of earlier authorised substances is not implicated. In support, the CVMP's strategy on AMR seeks to encourage the development of new antimicrobial VMPs for animals in order to avoid the over-reliance on a small number of substances which could accelerate the development of resistance, but also acknowledges that associated risks to public health must be fully considered.

### 2.1.2. AMEG opinion requested in 2017

In July 2017, the EC asked the EMA to update its 2014 advice on the impact of the use of antibiotics in animals on public health and animal health.

The terms of reference (TOR) in the mandate given to the EMA requests the following points to be addressed:

1. To revise the AMEG categorisation of antimicrobials (TOR 1)
2. To further elaborate on the proposed early hazard characterization (TOR 2)

## *2.2. Scope of the response*

The scope of the present document is related to the second part (TOR 2) of the European Commission request, relating to the early hazard characterisation.

The first part (TOR 1) of the European Commission request is published in a separate document (EMA/682198/2017).

The background note to the TOR mentions that the early hazard characterisation could be used to give an indication to future marketing authorisation applicants of the need for risk management measures to be applied to their new veterinary antimicrobial product. This knowledge could have an impact on the development of such products and improve the predictability of the regulatory outcome.

In addition, the early hazard characterisation could be used as a tool i) to assist decisions on whether an antimicrobial substance should be restricted or banned from cascade use in food-producing species and ii) in the preparation of a list of substances to be reserved for treatment of human infections only. The new Regulation on veterinary medicinal products includes provisions to address both these points (Official Journal of the European Union, 2019).

The Commission's mandate requests the EMA to provide:

- '*Detailed analysis of the benefits and risks of an early hazard characterisation: if the analysis would merit continuing with the proposal:*
    - *Further details on the procedure of the early hazard characterisation,*

- *Technical requirements of the early hazard characterisation*'

In order to avoid confusion with terminology used by Codex, the AMEG has chosen to use the term 'preliminary risk profile' (PRP) in place of 'early hazard characterisation'.

In the first part of the answer to this request, detailed below (chapter 3), the use of the preliminary risk profile to support the development of new antimicrobial veterinary medicinal products is addressed. Its possible use in the context of the new Regulation on veterinary medicinal products is briefly addressed in the second part (chapter 4).

# 3. Use of the preliminary risk profile in the development of antimicrobial veterinary medicinal products (VMPs)

## *3.1. Analysis of the benefits and risks of a preliminary risk profile: if the analysis would merit continuing with the proposal*

To assist with this part of the request a questionnaire was sent to the CVMP's interested parties/stakeholders who include potential future applicants for marketing authorisations for veterinary medicines. A copy of the questionnaire, sent to stakeholders on 13 March 2018, is included in Annex 1. The aims of the preliminary risk profile were included in the background to the questionnaire. Responses were received from Animalhealth Europe and EGGVP on 26 April 2018 and were largely supportive of the proposal.

### 3.1.1. Aims of preliminary risk profiling in regards to antimicrobial VMP development

The O'Neill report highlighted a need to encourage further development of antimicrobials for use in animals, in particular those substances found not viable for use in humans (O'Neill, 2015). At the same time, industry has commented that a barrier to the development of new veterinary antimicrobial products is the lack of a predictable regulatory process for antimicrobials and concern over the placing of restrictions that might unnecessarily limit the use of new products (du Marchie Sarvaas, 2015). Although the new Regulation on veterinary medicinal products gives opportunity for restrictions on the use of certain critical antimicrobials, at the same time it recognises the need to encourage and incentivise the development of new antibiotics for animals.

An aim of the PRP would be to encourage development of new antimicrobial VMPs by increasing the predictability of a positive regulatory outcome. The output of the PRP process as initially foreseen was high level advice on i) the concerns relating to potential public health risks from AMR in relation to veterinary use of an antimicrobial substance or medicinal product, and ii) the associated need for risk management measures (RMM).

Guidance would not be binding on a future marketing authorisation application (MAA): any future MAA should include a full AMR risk assessment addressing the specific conditions of use of an individual product, the outcome of which will be considered in the context of an overall benefit-risk assessment. If information on proposed target species and the intended pharmaceutical form were available for the PRP, this would allow more tailored risk profiling.

The expectation is that the assessment would be conducted before major investment in GLP/GCP studies; at least prior to clinical development of the product and possibly before application for an opinion on the maximum residue limits (MRLs) for a new active substance. Quantified benefits to

animal health, the impact of dosing regimen on resistance development and AMR in target pathogens would not be taken into account at this early stage. Detailed risk management measures (RMM) would also not be considered.

### 3.1.2. Benefits and risks of the preliminary risk profiling in regards to antimicrobial VMP development

Benefits:

- Increased regulatory predictability at early product development stage may encourage the pharmaceutical industry to develop new antimicrobials for animals, or to further develop existing antimicrobial VMPs.
- The PRP will help to identify gaps in the AMR risk assessment which should later be addressed in any subsequent MA application.
- Use of a parallel methodology to that to be used for consideration of restrictions on Cascade use, and for designating AMs to be reserved for human use, would help to ensure consistent decision-making.

Risks:

- Due to emergence of new unpredictable resistance mechanisms, and changes in importance of different AMs in human medicine, there is a risk that the PRP becomes outdated by the time a MA application is submitted.
- A precautionary approach would be a disincentive to product development.

Most of the comments received from stakeholders related to the need to have a flexible and efficient procedure. The possibility for involvement of expertise from a human medical background or collaboration with third countries was seen as a potential benefit.

## *3.2. Procedure for the Preliminary Risk Profiling in regards to antimicrobial VMP development*

Under the current legal framework, according to Article 56(3) of Regulation (EC) 726/2004) (Official Journal of the European Union, 2004), the CVMP's Scientific Advice Working Party (SAWP) has been established to provide recommendations to the CVMP on matters relating to VMPs including scientific advice to support product development in response to questions from prospective MA applicants. Including the PRP within this scope could be considered as the simplest way to implement this procedure.

The SAWP could involve members of the CVMP's Antimicrobials working party (AWP) and the Antimicrobial expert Group (AMEG) in order that a One Health approach is taken to the PRP and considering i) the emphasis on the public health aspects, ii) the need for consistency with the AMEG categorisation.

The Guidance for applicants requesting scientific advice (EMA/CVMP/SAWP, 2017) indicates that parallel advice may be sought from the Agency and the United Sates' FDA.

The current procedure for provision of scientific advice would take into account stakeholders' comments regarding the need to have a flexible and efficient procedure with clear timelines and ensuring confidentiality. The best available advice will be given based on the information provided by

the applicant and the existing state of play in regards to AMR and antimicrobial use at the time of the application. Advice will not be binding on either the applicant or the CVMP.

## *3.3. Technical requirements and scientific approach to the PRP in regards to antimicrobial VMP development*

### 3.3.1. Scope of antimicrobial substances/products/circumstances that may be considered in the PRP

- New antimicrobial classes, subclasses or substances not authorised in human or veterinary medicine
- Classes, sub-classes or substances authorised in human medicine but not yet authorised in veterinary medicine
- Substances authorised for use in companion animals for which authorisation is to be proposed in a food-producing species, or extension to a new food-producing species
- New combinations of antimicrobials where the individual substances are already authorised for use in veterinary medicine as mono-therapies
- Substances authorised for individual animal treatment in food-producing species for which future authorisation is intended for group oral treatment'
- Substances with a new antibacterial mode of action
- Substances used for overcoming resistance mechanisms

Other circumstances not listed could also fit within the framework.

### 3.3.2. Data availability

Stakeholders were asked at what stage of product development the PRP would be of most use and what data would be available at that stage. They advised that the target species, disease to be treated, (and potentially) route of administration and dose form are usually known from early on in product development and that the PRP would be most useful before major investment in GLP and GCP studies. Therefore available data may be limited to basic pharmacokinetic data, MIC studies, *in vitro* data on selection/development of resistance, and published data depending on use of the substance elsewhere.

In a scientific advice procedure the applicant is responsible for providing supporting data in relation to their application, although this may be supplemented by the CVMP with publicly available information, according to its own knowledge.

### 3.3.3. PRP supporting data requirements and assessment in regards to antimicrobial VMP development

Stakeholders requested that the PRP should allow flexibility of approach and, as available data may vary, three scenarios were considered depending of the stage of development/available information at the time of the request.

The identified supporting data and approach are based on an abridged version of the requirements in the CVMP's draft guideline on the assessment of the risk to public health from antimicrobial VMPs (EMA/CVMP/AWP, 2015).

290 **Table 1.** Elements to be considered in the PRP and examples of supporting data
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| Element of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| | **Substance/class only** → | **Substance/class + target animal species** → | **Substance/class + species + pharma form** |
| **Assumption to be made in the risk profiling** | The AM is intended for use in any target animal species, for any indication and in any pharmaceutical form. | The AM is intended for use in any pharmaceutical form applicable to the given target species. | The AM is intended for use in the given target species and given pharmaceutical form. |
| **Hazard identification** (resistance to the AM in zoonotic bacterial pathogens or resistance genes in commensal organisms that may be transferred to human pathogenic bacteria) | Antimicrobial class<br>Mechanism of action<br>Spectrum of activity | As shown left. | As shown left. |
| | Susceptible zoonotic or commensal bacterial spp.: *Campylobacter* spp., *Salmonella* spp., *E. coli, Enterococcus* spp., *Staphylococcus aureus*<br><br>Known mechanisms of resistance in each of these bacterial spp.<br><br>Occurrence of cross-resistance and co-resistance with other AM used in human medicine<br><br>Information may be taken from the AMEG categorisation assessment, where available | Bacterial spp considered as potential hazards can be tailored to the target animal spp. | Bacterial spp may be further tailored according to consideration of the route of administration and hence possibility of exposure, e.g. gastrointestinal microbiota etc., |
| **Release assessment** | Specific data not available.<br><br>Consider potential to be used in any food-producing or companion animal species, via any route of | Conditions of use which may be taken into account, e.g.<br>i) All food-producing spp.<br>ii) minor food-producing spp | In addition to information to left: Group/ individual, local/systemic, parenteral/oral administration. |

| Element of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| | administration. | iii) companion animal spp<br>iv) specified animal spp. / production type<br><br>If potential indications are provided (major/minor), this may impact on the extent of release.<br><br>Where available, other data as detailed in the AMR risk assessment GL may be provided. | Exposure of gastrointestinal microbiota or skin/mucosal flora to active substance/ metabolites |
| **Exposure assessment** | Specific data not available.<br><br>Consider potential for human exposure to hazard via both foodborne and direct contact routes. | Data on human consumption patterns of food produce from the target spp in the EU.<br>Where available, other data as detailed in the AMR risk assessment GL may be provided. | As shown left. |
| **Consequence assessment** | Importance of the antimicrobial in human medicine for treating the identified hazard(s) and severity of the disease.<br><br>Consideration of the availability of alternative antimicrobials in human medicine.<br><br>May be based on AMEG/WHO categorisation assessment, where available.<br><br>Extent of use of the AM substance/(sub)class in human medicine in the EU. | As shown to left. | As shown to left. |

| Element of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| **'Risk-risk' scenario** (i.e. consequence of restricting use in animals) | Specifics not known. | Impact on animal health of the proposed disease indications in the targets species.<br>Availability of alternative authorised treatments for use in animals for the disease(s) in question.<br><br>Impact on aquaculture/farming if restrictions are placed on the proposed new treatment. | As shown to left. |

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294 Assessment Process: Estimation of the risk to human health due to AMR

295 For each hazard identified, the release, exposure and consequence assessments are addressed
296 separately with key risks highlighted and an **overall estimation of the risks to human health due**
297 **to AMR** then drawn (Table 2):

298 **Table 2.** Assessment and integration of the risk profiling for each identified hazard

| Component of the PRP | Hazard identified e.g. | | | | | |
|---|---|---|---|---|---|---|
| | *Campylobacter* spp. | *Salmonella* spp. | *E. coli* | *Enterococcus* spp. | *S. aureus* | Other |
| **Release** (tailored to species +/- formulation where known) | | | | | | |
| **Exposure** (tailored to species, where known) | | | | | | |
| **Consequence** – importance in human medicine for the corresponding infection. | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| **Overall estimation of risks to human health due to AMR** | | | | | | |

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Additional considerations: The consequence to animal health and the livestock industry of restricting use of the antimicrobial medicine in animals is also taken into consideration ('risk-risk' scenario).

### 3.3.4. Outcomes of the PRP for antimicrobial VMP development

Based on the overall estimation of the risks to human health due to AMR (Table 2) and considering the 'risk-risk', Table 3 shows the outcomes of the PRP according to the level of data provided:

**Table 3.** Outcomes of the PRP according to the level of data provided

| Substance only | Substance + target animal species/(indication) | Substance + species/(indication) + pharmaceutical form |
|---|---|---|
| Based on the identification of AMR hazard(s), the potential for transfer of AMR from animals to humans and the importance of the AM to human medicine, a high level estimate can be made of the risk to human health (Table 2).<br><br>An aim will be to identify specific areas of concern and data gaps to be addressed in a future MAA, as well as options for high level RMM, e.g. it may be proposed to restrict to 'treatment' use only (not metaphylaxis), or to limit the route of administration.<br><br>The PRP conducted on behalf of a future MA applicant would not be used to place a substance on the 'Reserved for human use' list; however, attention would be drawn to the need to satisfactorily address the highlighted concerns to enable a positive benefit-risk to be reached in an MA application. | In addition to outcomes to the left:<br><br>The risk estimation can be further refined according to the possible hazards present in the given target species, the opportunity for foodborne and/or contact routes of transmission of AMR, the potential size of the animal population exposed, etc.<br><br>This can be balanced against the risks to animal health and the livestock industry if restrictions are placed on the new treatment (risk-risk).<br><br>More detailed consideration can be given to RMM, e.g. restricting to/from use in certain species, or use in certain indications. | In addition to outcomes to the left:<br><br>The risk estimation can be further refined according to the impact of the formulation on the 'release' of the hazard from the target animal population. |

A flexible approach will be taken according to the data supplied by the applicant and therefore the outcomes may vary from those given above.

# 4. Use of the preliminary risk profile in the context of the new Regulation on veterinary medicinal products

## *4.1. Legislative background*

Amongst the considerations in the new Regulation on veterinary medicinal products that support measures to address the risk from AMR, a need is foreseen to restrict the use in animals of antimicrobials that are critical for preventing or treating life-threatening infections in humans. It is proposed that certain antimicrobials should be reserved for use in humans only in order to preserve their efficacy for the treatment of infections in humans.

In addition, it is suggested that off-label use of certain new or critically important antimicrobials for humans should be restricted in the veterinary sector and, if necessary, conditions should be laid down to restrict use of veterinary medicinal products that is not in accordance with the authorised conditions of use as detailed in the SPC.

When considering restrictions on the use of certain antimicrobials in animals, an adapted PRP may be a useful tool to take account of the AMR risk to public and animal health relating to such use. In addition, information on possible cascade uses, the availability of alternative treatments for these conditions and any impact on animal health and welfare, aquaculture and farming if the condition cannot be treated should be taken into account.

## *4.2. Analysis of the benefits and risks of the PRP in the context of decisions on antimicrobials to be reserved for human use or having conditions placed on off-label use*

Benefits of the Preliminary Risk Profile:

- Could provide a methodology and criteria to be used or further developed to support decisions on AMs to be reserved for human use, or conditions to be applied for off-label use.
- Methodology could also assist National Competent Authorities in development of national policy restricting or prohibiting the use of certain AM on their territory.
- Published assessments could assist veterinary professionals preparing treatment guidelines and/or applying the Cascade by providing guidance on human and animal health risks.
- A transparent and evidence-based methodology for placing restrictions on Cascade use may achieve a better balance between the need to protect public and animal health from AMR versus the risk to animal health and welfare due to lack of available antimicrobial VMPs.

Risks:

- Further restrictions on Cascade use could reduce availability of AMs (e.g. for MUMS) and impact animal health and welfare, in particular where there is a limited evidence-base to conclude on the AMR risks associated with such use and a conservative approach is taken in the PRP.

## *4.3. Technical requirements and scientific approach*

### 4.3.1. Scope of antimicrobial substances/classes that may be considered

Consideration of antimicrobials to be reserved for human use:

- New antimicrobial (sub)classes or substances not yet authorised in human or veterinary medicine, as these come to light.
- (Sub)classes or substances authorised in human medicine but not yet authorised in veterinary medicine.
- (Sub)classes or substances authorised in veterinary medicine for which a serious AMR risk to public health due to use in animals is identified post-authorisation.

Consideration of antimicrobials for which conditions should be placed on cascade use

- (Sub)classes or substances authorised in human medicine but not authorised in veterinary medicine for which a potential serious AMR risk to public health due to use in animals is identified.
- (Sub)classes or substances authorised in veterinary medicine for which a serious AMR risk to public health due to use in animals is identified post-authorisation.

### 4.3.2. PRP supporting data requirements and assessment

The identified supporting data and proposed approach are based on the AMEG's criteria for antimicrobial categorisation and an abridged version of the requirements in the CVMP's draft *Guideline on the assessment of the risk to public health from antimicrobial VMPs*.

For antimicrobials to be reserved for human use only, the assessment would be performed taking account of the antimicrobial class/substance alone. When addressing cascade use, consideration might be given to substance/class alone, or also to the target species and pharmaceutical form relating to a specific (group of) product(s).

**Table 4.** Elements to be considered in the PRP for use in decisions on antimicrobials to be reserved for human use or having conditions placed on off-label use
The blue text below indicates the additional data required to those in Table 1.

| Component of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| | **Substance only (Reserved List and Cascade conditions)** | **Substance + target animal species (Cascade conditions)** | **Substance + species + pharma form (Cascade conditions)** |
| Assumption to be made in the risk profiling | The AM is intended for use in any target animal species, for any indication and in any pharmaceutical form. | The AM is intended for use in any pharmaceutical form applicable to the given target species. | The AM is intended for use in the given target species and given pharmaceutical form. |
| Hazard identification<br>Resistance to the AM in zoonotic bacterial pathogens, target | Antimicrobial class<br>Mechanism of action<br>Spectrum of activity | As shown left. | As shown left. |

| Component of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| animal pathogens or resistance genes in commensal organisms. | Susceptible bacterial spp. of concern to human health e.g. *Campylobacter* spp., *Salmonella* spp., *E. coli*, *Enterococcus* spp., MRSA<br><br>Spectrum of activity in regards to important target animal pathogens.<br><br>Known mechanisms of resistance in each of these bacterial spp.<br><br>Occurrence of cross-resistance and co-resistance with other AM used in human and/or veterinary medicine<br><br>Information may be taken from the AMEG categorisation assessment, where available. | Bacterial spp considered as potential hazards can be tailored to the target animal spp. | Bacterial spp considered as potential hazards may be further tailored according to consideration of AM exposure to gastrointestinal microbiota etc., where known. |
| Release assessment | Specific data not available.<br><br>Consider potential to be used in any food-producing or companion animal species, via any route of administration. | Conditions of use which may be taken into account, e.g.<br>i) all food-producing spp.<br>ii) minor food-producing spp<br>iii) companion animal spp<br>iv) specified animal spp. /production type.<br><br>Indications (major/minor) may impact on the extent of release. | In addition to information to left:<br>Group or individual animal medication<br><br>Exposure of gastrointestinal microbiota or skin/mucosa to active substance/metabolites |

| Component of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| | | Data as indicated in the AMR risk assessment GL may be considered. | |
| Exposure Assessment | Specific data not available.<br><br>Consider potential for human and animal exposure to hazard via both foodborne and direct contact routes. | Data on human consumption patterns of food produce from the target spp. in the EU.<br>Where available, other data as detailed in the AMR risk assessment GL.<br><br>Data on human consumption patterns of food product from species applicable for cascade use in the EU. | As shown left. |
| Consequence assessment | Importance of the antimicrobial in human medicine for treating the identified hazard and severity of the disease.<br><br>Consideration of the availability of alternative antimicrobials in human medicine.<br><br>May be based on AMEG/WHO categorisation assessment, where available.<br><br>Extent of use of the AM substance/class in human medicine in the EU.<br><br>Importance of the | As shown to left.<br><br>As shown left. | As shown to left.<br><br>As shown left. |

| Component of the PRP | Information required, according to level of assessment | | |
|---|---|---|---|
| | antimicrobial to animal health when used as authorised (where applicable). May be based on AMEG/OIE categorisation assessment.<br><br>Possible AMR risks to animal health in general due to cascade use (where applicable*). | | |
| Potential treatment benefits for animals | Information on possible cascade uses (target spp., indications) | Potential therapeutic need according to the proposed targets species and indications.<br><br>As shown left. | As shown to left.<br><br>As shown left. |
| 'Risk-risk' factors | Availability of alternative treatments for use in animals for the disease(s) in question.<br><br>Impacts on farming/aquaculture due to inability to treat proposed target species and indications. | As shown left. | As shown left. |

373 *Not necessary for consideration of 'Reserved List'.
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375 Assessment Process: Estimate of risk to human and animal health due to AMR

376 For each hazard identified, the release, exposure and consequence assessments are addressed
377 separately with key risks highlighted and an **overall estimation of the risks to human and animal**
378 **health due to AMR** then drawn (Table 5):

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**Table 5.** Assessment and integration of the risk profiling for each identified hazard

| **Component of the PRP** | **Hazard identified e.g.** | | | | | |
|---|---|---|---|---|---|---|
| | *Campylobacter* spp. | *Salmonella* spp. | *E. coli* | *Enterococcus* spp. | *Staphy-lococcus aureus* | Other (including AMR in target animal pathogens) |
| **Release** (tailored to species +/- formulation where known) | | | | | | |
| **Exposure** (tailored to species, where known) | | | | | | |
| **Consequence** – importance in human medicine for the corresponding infection. Importance to animal health for authorised indications. | N/a | | | | | |
| | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| **Overall estimation of risks to human and animal health due to AMR** | | | | | | |

Additional considerations: In addition to the risk estimation above, attention would also have to be given to the 'risk-risk' scenario by considering information on possible cascade uses, the availability of alternative treatments for these conditions and any impact on animal health and welfare, aquaculture and farming if the condition cannot be treated.

Further consideration of the application of the PRP in relation to the 'Reserved List' and conditions to be placed on cascade use will be dependent on the mandates from the Commission to the EMA in relation to the implementing and delegated acts referenced in the new Regulation on veterinary medicinal products.

# Annex 1 - Questionnaire for Stakeholders (sent on 21 March 2017)

# 1. Background

## *1.1. AMEG opinion requested in 2013*

In 2014, following a request from the European Commission, the EMA published advice on the impact on public health and animal health of the use of antibiotics in animals. Part of this advice was to consider the impact on AMR of the authorisation of new classes of veterinary antimicrobials, and if there is a need to restrict or ban the use in animals of certain new classes that are currently not authorised.

The advice concluded in response that a specific risk assessment would be needed for each new substance/class to assess its importance to human health and the risk of transfer of resistance from treated animals to humans. In addition, it was recognised that in order to obtain a marketing authorisation for a new VMP containing such a substance, this risk assessment would be tailored to the conditions of use of the product (e.g. target species, indications) and form part of an overall benefit-risk assessment that would also take into account the treatment benefit of the product for animal health.

Further to this conclusion, it was however noted that a substance-related assessment ('early hazard characterisation') could be of value to provide an indication to potential applicants for marketing authorisations for new antimicrobial VMPs (for food-producing species) as to the potential AMR risks to public health and the need for risk management measures. This concept received support from attendees at a workshop held by the Commission in November 2015.

## *1.2. AMEG opinion requested in 2017*

In July 2017, the Commission requested the EMA to update its opinion on the categorisation of antimicrobials (TOR 1) and to give an advice on an early hazard characterisation (TOR 2) [2]. The background note to the terms of reference mentions that the early hazard characterisation could be used to give an early indication to marketing authorisation applicants of the need for risk management measures for new veterinary antimicrobial products and thus impact their development. In addition, it could assist in the preparation of a list of substances to be reserved for human infections only.

### TOR 2

The Commission requests the EMA to provide:

- 'Detailed analysis of the benefits and risks of an early hazard characterisation; if the analysis would merit continuing with the proposal:
  - Further details on the procedure of the early hazard characterisation,
  - Technical requirements of the early hazard characterisation'

[2] Link to AMEG request from the European Commission in July 2017
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/07/WC500232322.pdf

# 2. Proposed aims of an early hazard characterisation/ preliminary risk profiling in regards to antimicrobial VMP development

The O'Neill report [3] highlighted a need to encourage further development of antimicrobials for use in animals, in particular those found not viable for use in humans. At the same time, industry has commented that a barrier to the development of new veterinary antimicrobial (products) is the lack of a predictable regulatory process and concern over the restrictions on use that might unnecessarily limit the use of new products [4].

An aim of the **'Preliminary Risk Profile'**[5] (**PRP**) would be to encourage development by industry of new antimicrobial VMPs for use in animals. The outcome of the process would be to provide high level advice i) on the concerns relating to potential **public health** risks from AMR in relation to an antimicrobial substance/product, and ii) the associated need for high level risk management measures (RMM), including potential refusal to authorise use in animals.

Is likely that guidance would not be binding on a future marketing authorisation (MA) application which would consider a full AMR risk assessment addressing the specific conditions of use of an individual product in the context of an overall benefit-risk assessment. If information on proposed target species and pharmaceutical from were available, this would allow more tailored risk profiling (see below).

The expectation is that the assessment would be conducted at least prior to clinical development of the product and possibly before application for an opinion on the maximum residue limits. Benefits to animal health, the impact of the dosing regimen on AMR development and AMR in target pathogens would not be taken into account at this early stage. Detailed RMM would also not be considered.

# 3. Objective of this questionnaire

The AMEG would like to seek the initial views of the pharmaceutical industry on the questions below relating to a possible preliminary risk profiling (PRP)

# 4. Potential scope of substances/products/circumstances to be considered:

- New classes/substances, not authorised in human or veterinary medicine
- Classes/substances, authorised in human medicine, not yet authorised in veterinary medicine
- Substances authorised for use in companion animals for which authorisation is to be proposed in a food-producing species, or extension to a new food-producing species.
- New combinations of antimicrobials where the individual substances are already authorised for use in veterinary medicine as mono-therapies.
- Substances authorised for individual animal treatment in food-producing species for which future authorisation is intended for group oral treatment

[3] O'Neill J. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste. The review on antimicrobial resistance. December, 2015

[4] du Marchie Sarvaas, 2015, IAHJ Research & Development. Vol 2, Issue 1. Investment in New Veterinary Antibiotics: Barriers, Consequences and Solutions. http://animalhealthmedia.com/investment-in-new-veterinary-antibiotics-barriers-consequences-and-solutions/

[5] It is proposed that the terminology may be changed from 'early hazard characterisation' to 'Preliminary Risk Profile (PRP) to avoid confusion with terminology used by Codex.

**Question 1**

**Please comment on the scope of substances/circumstances to be considered.**

# 5. Consideration of technical requirements and potential outputs of the PRP

It is anticipated that the PRP would be based on a limited dataset that would be provided by an applicant. The output of the PRP and associated level of certainty would be dependent on the quality of the data provided. The methodology has yet to be determined, but the schema below gives an indication of the information required for different levels of risk profiling.

| ***Level of information available*** | ***Output*** |
|---|---|
| ***Substance only***<br>*Information to be supplied on antimicrobial class, spectrum of activity, known resistance mechanisms, occurrence of co-/cross-resistance.*<br>*Information on the importance and need of the substance in human medicine, potential for transfer of AMR from animals to humans* | *High level profiling considering the need to reserve the substance for use in humans only, assuming potential use in any animal spp.* |
| ***Substance + target species***<br>*Additional information to be supplied relating to use in e.g.*<br>*i) All food producing species*<br>*ii) Minor food producing spp.*<br>*iii) Companion animal spp.*<br>*iv) Specified individual spp.* | *The profiling could be refined taking into account possible hazards and exposure related to the proposed target animal species, assuming administration by any route. Consideration on need to restrict from use in the given spp.* |
| ***Substance + target species + pharmaceutical form***<br>*Additional information to be supplied relating to pharmaceutical form and e.g. to group or individual animal treatment, exposure of gastrointestinal microbiota* | *The profiling could be refined taking into account potential exposure of zoonotic and relevant commensals, and the potential volume of use of the given formulation. Consideration on the need to restrict from administration by given route/formulation.* |

**Question 2**

**a) At what stage of product development would the PRP be of help:**

**Knowledge of antimicrobial substance only?**

**Knowledge of antimicrobial substance + proposed target species (as above)?**

**Knowledge of antimicrobial substance + proposed target species + proposed pharmaceutical form?**

**b) At each stage of product development, what information is likely to be available from a potential applicant?**

# 6. Analysis of the benefits and risks of the PRP

Some initial considerations on the possible benefits and risks of the PRP are given below.

| Benefits of the Preliminary Risk Profile | Risks |
|---|---|
| Increased regulatory predictability at early product development stage may encourage pharma industry to develop new antimicrobials for animals or further develop existing antimicrobial VMPs | A legal basis for future MA applicants to submit a request for a PRP should be identified.<br><br>Due to emergence of new unpredictable resistance mechanisms, and changes in importance of different AMs in human medicine, assessments may require regular review (e.g. 5 yearly). |

**Question 3**

**Please comment on any benefits and risks you foresee for the PRP.**

**Question 4**

**Please suggest any ways in which the concept could be improved with the goal of encouraging the development of new veterinary antimicrobial products, or alternatively advise if the concept does not merit development.**

# Annex 2 - References


du Marchie Sarvaas, C., 2015. 'Investment in New Veterinary Antibiotics: Barriers, Consequences and Solutions', International Animal Health Journal, Vol. 2 (1), pp.26-28.

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