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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 antimicrobial veterinary medicinal products

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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.

In a new mandate received in 2017, the Commission requested the EMA to further elaborate on the proposed early hazard characterization.

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 characterisation'.

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 support 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, 2015a), 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 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 to farming/aquaculture 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.

According to Regulation EU 2019/6 (Official Journal of the European Union, 2019), 'antimicrobials' include antibiotics, antivirals, antifungals and anti-protozoals. The PRP has been developed primarily with antibacterial substances in mind, but in principle could also be applied at high level to other types of antimicrobial.

Antimicrobials included in the list of antimicrobials reserved for use in humans according to Regulation (EU) 2019/6 article 37(5) will not be eligible for consideration by the PRP process (see chapter 4).

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 animal 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[1].
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

[1] Article 11 of Directive 2001/82/EC and Articles 107, 113 and 114 of Regulation (EC) 2019/6. Legislation includes provisions which, when no suitable authorised product is available and under exceptional circumstances, allow 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.

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 will be published in a separate document (EMA/CVMP/CHMP/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.

Although the draft of this document initially addressed the potential use of the early hazard characterisation to consider restrictions on antimicrobial use introduced under Regulation EU 2019/6, this aspect is now being addressed under a new Commission mandate.

The Commission's 2017 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 characterisatio*n'

In order to avoid confusion with terminology used by Codex, the AMEG has chosen to use the term '<u>preliminary</u> risk profile' (PRP) in place of 'early hazard characterisation'. The PRP should not be confused with the 'preliminary foodborne AMR risk profile' detailed under Codex CAC/GL 77-2011, which is intended to identify an AMR food safety issue.

Regulation (EU) 2019/6 (Official Journal of the European Union, 2019) defines an *antimicrobial* as 'any substance with direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.' As Article 37 of Regulation EU 2019/6 relates to antimicrobial substances, an application for a PRP may be made for any substances falling within this definition. However, the PRP was primarily conceived with antibacterial substances in mind; data requirements may not be fully applicable to other types of antimicrobial although in principle the approach may be followed at high level.

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 European Group for Generic Veterinary Products (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 antimicrobials considered critical for the treatment of human infections, it also 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 the 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 based on the PRP would not be binding on a future marketing authorisation application (MAA): any future MAA should include an 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, as required under applicable legislation.

The expectation is that the assessment would be conducted before major investment in GLP or 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. If information on proposed target species and the intended pharmaceutical form were available for the PRP, this would allow more tailored risk profiling.

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.

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.
- The fact that the PRP outcome will be non-binding may be a disincentive to some applicants.

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 States' 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. In addition, there is provision within the current scientific advice procedure for direct (face-to-face) engagement between applicants and the SAWP. 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.

If a marketing authorization application is not received within 4 years of issue of the advice, or if there is a significant change in the AMR situation (e.g. identification of an important new AMR mechanism), then the advice may be updated at the applicant's request.

Subsequent requests for advice based on the same substance/product under different conditions of use e.g. new species, indications or formulation, would require a new PRP in the context of the prevailing circumstances (e.g. regarding AMR situation, clinical need) at the time of the application.

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 mode of action
- Substances used for overcoming resistance mechanisms

Other circumstances not listed could also fit within the framework.

Substances or classes of antimicrobials designated for human use only according to Regulation (EU) 2019/6 article 37(5) will not be eligible for consideration by the PRP process.

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 animal 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, 2015a). Reference can be made to this document for further information or explanation, although the PRP is intended to be a preliminary assessment based on more limited data.

Table 1. Elements to be considered in the PRP and examples of supporting data

Element of the PRP	Information required, according to level of assessment (AM = antimicrobial substance)		
	Substance / class only →	**Substance / class + target animal species** →	**Substance / class + animal species + pharmaceutical 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 animal species.	The AM is intended for use in the given target animal species and given pharmaceutical form.
Hazard identification Resistance to the AM and/or resistance determinants to the AM in zoonotic pathogens and/or commensal organisms that may be transferred to humans or to organisms potentially pathogenic to humans.	Antimicrobial class Mechanism of action Spectrum of activity	As shown left.	As shown left.
	Details of susceptible zoonotic or commensal organisms e.g. *Campylobacter* spp., *Salmonella* spp., *E. coli, Enterococcus* spp., *Staphylococcus* spp. Known mechanisms of resistance in each of these bacterial spp/organisms. Occurrence of cross-resistance and co-resistance with other AM used in human medicine.	Bacterial spp/organisms considered as potential hazards can be tailored to the target animal spp. (EMA/CVMP/AWP, 2015b)[2]	Bacterial spp/organisms may be further tailored according to consideration of the route of administration and hence possibility of exposure, e.g. gastrointestinal microbiota etc.

[2] For companion animals see CVMP Reflection paper on the risk of antimicrobial resistance transfer from companion animals EMA/CVMP/AWP/401740/2013

Element of the PRP	Information required, according to level of assessment (AM = antimicrobial substance)		
	Selection of multi-resistant organisms. Information may be taken from the AMEG categorisation assessment, where available		
Release assessment	Specific data not available. 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. i) All food-producing spp. ii) minor food-producing spp iii) companion animal spp iv) specified animal spp. / production type If potential indications are provided (major/minor), this may impact on the extent of release. Where available, other data as detailed in the AMR risk assessment guideline may be provided.	In addition to information to left: group/ individual, local/systemic, parenteral/oral administration. Exposure of gastrointestinal microbiota or skin/mucosal flora to active substance/ metabolites
Exposure assessment	Specific data not available. 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. Where available, other data as detailed in the AMR risk assessment guideline may be provided.	As shown left.
Consequence assessment	Importance of the antimicrobial in human medicine for treating the identified hazard(s), or	As shown to left.	As shown to left.

Element of the PRP	Information required, according to level of assessment (AM = antimicrobial substance)		
	organisms resistant due to resistant determinant transfer from the identified hazard(s), and severity of the disease. Consideration of the availability of alternative antimicrobials in human medicine. May be based on AMEG or WHO[3] categorisation assessment, where available. Extent of use of the AM substance/(sub)class in human medicine in the EU.		
'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. Availability of alternative authorised treatments for use in animals for the disease(s) in question. Reference may be made to information in the AMEG categorisation. Other impacts such as on aquaculture/farming if restrictions are placed on the proposed new treatment.	As shown to left.

[3] The AMEG categorisation is based on that of WHO taking an EU perspective and therefore should be used as the first option. However, the WHO categorisation (where available) may be used for classes not yet included in the AMEG list.

Assessment Process, Part 1: Estimation of the risk to human health due to AMR

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

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.	*Staphylococcus* spp.	Other
Release (tailored to animal species +/- formulation where known)						
Exposure (tailored to animal species, where known)						
Consequence – importance in human medicine.	⬇	⬇	⬇	⬇	⬇	⬇
Overall estimation of risks to human health due to AMR						

Reference may be made to the CVMP's draft guideline on the risk assessment of antimicrobial VMPs to assist with the interpretation of the data, according to the extent of the data provided.

Assessment process, Part 2: Consideration of the consequence to animal health and farming/aquaculture of restricting use of the antimicrobial medicine in animals ('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 + animal 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). An aim will be to identify specific areas of concern and data gaps to be addressed in a future marketing authorisation application, as well as options for high level risk management measures, e.g. it may be proposed to restrict to 'treatment' use only (not metaphylaxis), or to limit the route of administration. If proposed RMM result from data gaps/uncertainties at the time of the PRP, this will be indicated. The PRP conducted on behalf of a future marketing authorisation 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 facilitate a positive benefit-risk to be reached in a marketing authorisation application.	In addition to outcomes to the left: 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. This can be balanced against the risks to animal health and farming/aquaculture if restrictions are placed on the new treatment (risk-risk). More detailed consideration can be given to risk management measures, e.g. restricting to/from use in certain species, or use in certain indications.	In addition to outcomes to the left: 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.

The PRP will not lead to confirmation of an 'acceptable level' of AMR risk for the substance/product. Such a conclusion could only be reached following consideration of a comprehensive risk assessment submitted in the context of a specific MA application and when any identified risks have been considered in light of the documented benefits of the product.

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

Amongst the considerations in the new Regulation (EU) 2019/6 on veterinary medicinal products (Official Journal of the European Union, 2019) that support measures to address the risk from AMR, a need is foreseen 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.

According to Article 37(4), the EMA is mandated by delegated acts to establish criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans in order to preserve the efficacy of those antimicrobials. Criteria to be defined are not limited to antimicrobials that have not yet been authorised for the veterinary market but may also be applied to existing veterinary products Article 152(1). Founded on criteria related to this mandate, substances or classes of antimicrobials that should be reserved for human use will be designated by implementing acts under Article 37(5). For veterinary products containing these antimicrobials a marketing authorisation (MA) will be refused according to Article 37(3). Designation of antimicrobials reserved for humans will automatically lead to their use in animals being prohibited.

Based on the provisions laid down in Regulation (EU) 2019/6, antimicrobials included in the list of antimicrobials reserved to humans according to Article 37(5) will not be eligible to the PRP process.

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) [4]. 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'

[4] 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 [5] 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 [6].

An aim of the **'Preliminary Risk Profile'**[7] (**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.

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

[6] 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/

[7] 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.

- Substances authorised for individual animal treatment in food-producing species for which future authorisation is intended for group oral treatment

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 *Information to be supplied on antimicrobial class, spectrum of activity, known resistance mechanisms, occurrence of co-/cross-resistance.* *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 *Additional information to be supplied relating to use in e.g.* *i) All food producing species* *ii) Minor food producing spp.* *iii) Companion animal spp.* *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 *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. 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.

EMA/AMEG, 2014. 'Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Answer to the second request from the EC (ranking of antibiotics); Answer to the third request from the EC (new antibiotics); Answer to the fourth request from the EC (risk mitigation options) (EMA/381884/2014)', https://www.ema.europa.eu/documents/other/answers-requests-scientific-advice-impact-public-health-animal-health-use-antibiotics-animals_en.pdf

EMA/CVMP/AWP, 2015a. '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 (EMA/CVMP/AWP/706442/2013)', https://www.ema.europa.eu/en/assessment-risk-public-health-antimicrobial-resistance-due-use-antimicrobial-veterinary-medicinal

EMA/CVMP/AWP, 2015b. 'Reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP/401740/2013)', https://www.ema.europa.eu/en/risk-antimicrobial-resistance-transfer-companion-animals

EMA/CVMP/SAWP, 2017. 'Guidance for applicants requesting scientific advice (EMEA/CVMP/SAWP/172329/2004 Rev. 5)', https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-companies-requesting-scientific-advice-veterinary_en.pdf

O'Neill, J., 2015. 'Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste - The Review on Antimicrobial Resistance - December 2015', http://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf

Official Journal of the European Union. 2004. Regulation No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. In http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1416477684261&uri=CELEX:32004R0726.

Official Journal of the European Union, 2019. 'Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC', https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN