27 June 2019
EMA/CVMP/CHMP/201533/2019
Committee for Medicinal Products for Veterinary Use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on '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' (EMA/CVMP/CHMP/682199/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Federation of Veterinarians of Europe (FVE)
2	Association of Veterinary Consultants
3	Danish Medicines Agency (DKMA)
4	Finnish Food Authority
5	Public Health Agency of Canada
6	Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	FVE welcomes this document on preliminary risk profiling (before called early hazard characterization) for new antimicrobials before applying for marketing authorisation. We welcome its aim namely to consider AMR risk from the new substance and whether risk management measures (e.g. no use in the cascade or no oral use) will be needed in order for industry to have more predictability at early product development stage. We hope this could provide some clarity and incentives to encourage the development of new antimicrobials. To illustrate the way this concept would work, it would be beneficial to include some scenarios.	Thank you for this comment. This will not be possible in the given timeframe.
2	This is an interesting and potentially valuable Guideline, which might help the Animal Health Industry (AHI) assess the risks when developing a new antibiotic. The goal posts have moved incredibly over recent years and thus this Preliminary Risk Profile (PRP) is necessary and will go a long way to enable the AHI to make a decision on whether to develop a new antimicrobial or not. In the meeting last year, in September 2018, tiamulin was used as an example to carry out a PRP (Alban et al., 2017), in the light of the potential introduction of a new antibiotic in the same pleuromutilin family, lefamulin, for the treatment of respiratory infections in man. Working through the process identified a number of developments and also a shortfall in certain information, such as the development of transferable resistance genes and their incidence, significance and	

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	potential risk to man. In the EMA consultation document (19 July 2018) there was a numerical definition of risk, based on the EFSA system, which was most helpful in quantifying that risk and it was different from the numbers used in Alban et al. (2017). In the current Guideline document there is no reference to this interpretation of limit definitions for release and exposure and it is requested that such a quantitative assessment be re-instated:	

Ref	Very low	Low	Medium	High
EMA, 2018 (EFSA)	≤1%	>1-10%	>10-20%	>20%

This makes the PRP easier to interpret. In many cases, a potentially transmissible resistance gene has been identified as being present, in a particular organism, such as livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), but information on the precise incidence of that gene and therefore its relative significance and potential risk is often not available. In the case of *cfr* or *vga* genes, regarding pleuromutilin resistance risk, the incidence might only be 'very low' or 'low'. Peeters et al. (2015) demonstrated the presence of 1 (0.47%) *cfr* gene and 4 (1.9%) *vga*(A) genes in 211 Belgian MRSA isolates from pigs and Sönksen (2019 – Personal communication) reported that in a survey of 257 Danish LA-MRSA CC398 isolates there were zero (0%) *cfr* genes found and only 1 (0.4%) *vga* gene. It should be remembered that linezolid use in man is the primary selector for *cfr* gene resistance in man and the cross-resistance to tiamulin was shown to be unidirectional to tiamulin and

The CVMP's draft GL on the Risk Assessment of Antimicrobial VMPs EMA/CVMP/AWP/706442/2013 may be used – and is cited - as a cross-reference for the PRP. This

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	not the other way, tiamulin to linezolid (Miller et al, 2008). This is an important example that a gene may be present but its significance and risk of selection and transmission needs to be addressed. In this case, the significance can be determined as 'very low' for the *cfr* gene and 'low to very low' for the *vga* gene and therefore the risk of transmission of that gene to man is also likely to be 'low to very low'. As more data is produced the uncertainty can be changed and the reliability of the assessment and decision can be increased. This would be especially helpful in the early stages of development, when data may be limited. We are not sure why the quantitative assessment was removed from the latest draft but we would encourage that its re-instatement be considered. **References:** Alban, L., Ellis-Iversen, J., Andreasen, M., Dahl, J. and Sönksen, U.W. (2017) Assessment of the risk to public health due to use of antimicrobials in pigs – an example of pleuromutilins in Denmark. Frontiers in Veterinary Science, 4, 74 doi:10.3389/vets.2017.00074 EMA (19 July 2018) EMA/CVMP/AWP/706442/2013. 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 2) Miller, K., Dunsmore, C.J., Fishwick, C.W.G. and Chopra, I. (2008) Linezolid and tiamulin cross-resistance in Staphylococcus aureus by point mutations in the peptidyl transferase center. Antimicrobial Agents and Chemotherapy, 52, 5, 1737-1742. Peeters, L.E.J., Argudin, M.A., Azadikhah, S. and Butaye, P. (2015)	includes a qualitative 'scaling' for several of the risk indicators. However since the former document is still under revision by CVMP (work on completion of this guideline has been temporarily suspended under the EMA's business continuity plan), it is preferred not to include the specific limit definitions in the PRP document in order to avoid any inconsistency arising between the two documents. It was also preferred not to include specific scales in the PRP document as they may not be applicable to the data available at this early stage.

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	Antimicrobial resistance and population structure of *Staphyococcus aureus* recovered from pig farms. Veterinary Microbiology, 180, 151-156.	
3	The Danish Medicines Agency does not support the 'Preliminary Risk Profiling for new antimicrobials' in its current form and content. It is assumed that the 'Preliminary Risk Profiling' document was intended for the evaluation of antimicrobials substances that could be intended for companion animals and/or food animals. However, it is unclear as to why the food animal considerations for the 'Preliminary Risk Profiling' document does not follow the *Codex texts on foodborne Antimicrobial resistance - Codex Alimentarius.* Furthermore, there are aspects of the purpose/s of the 'Preliminary Risk Profiling' document that are unclear. Is the 'Preliminary Risk Profiling' document only intended for the initial application phase of a new antimicrobial? For example, if a risk mitigation measure identified was to lead to a non-binding restriction the indication of the product, then it is unclear if the 'Preliminary Risk Profiling' document would also used for any future variation procedures of the new antimicrobial? There is no point in suggesting a restricted indication of the product if future variations could come forward to expand the	Thank you for the extensive comments. While certain changes to the text have been made to address a number of very specific comments, others comments have not resulted in any change to the text. Indeed, a number of the comments made/concerns expressed appear to indicate a misunderstanding of the origins and basic purpose of the risk profiling document or are based on statements that have been read and interpreted out of context. Responses to the specific comments/concerns raised are included below It is clearly stated that the approach is based on the CVMP's draft GL on the Risk Assessment of Antimicrobial VMPs EMA/CVMP/AWP/706442/2013, which takes account of the Codex methodology but is mostly based on OIE methodology to facilitate alignment with models used in other regulatory jurisdictions and due to the particular applicability of the 'release assessment' step to the risk assessment for VMPs. The scope of the PRP for VMP development is outlined in section 3.3.1. These are the main situations in which a PRP is envisaged, but as stated 'Other circumstances not listed could also fit the framework'. The advice is intended to be non-binding and it has been further clarified in section 3.2.

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	indication/s. There is relevant text to highlight in the Commission's mandate letter of requests to EMA to provide: "The EMA response to the third EC request indicated that the risk assessment of new antimicrobial substances for use in food-producing species should be reinforced, and that *"One of the possible options would be to introduce an early hazard characterisation, addressing the risk to public health from antimicrobial resistance (AMR), to be assessed prior to the submission of a MAA."* Terms of Reference • '*Detailed analysis of the benefits and risks of an early hazard characterisation: if the analysis would merit continuing with the proposal:* o *Further details on the procedure of the early hazard characterisation,* o *Technical requirements of the early hazard characterisation*' There are serious concerns that the mandate/scope for the early hazard characterization is not fulfilled, including the initial reasons for its conception in "*… addressing the risk to public health from antimicrobial resistance (AMR) …*". This early hazard characterization ('Preliminary Risk Profiling') document appears to be based on a questionnaire only sent to pharma industry and not sent to dedicated public health organisations (e.g. WHO, FAO, OIE). Recognised codices specifying risk assessments of AMR from food animals from dedicated public health organisations (e.g. WHO, FAO, OIE) do not appear to have been considered in this document.	that subsequent requests for advice based on the same substance/product would require a new PRP in the context of the prevailing AMR circumstances at the time of the application. This also applies to the AMR risk assessment for future variation applications. A stated aim of the PRP (as indicated also in the mandate) is to provide incentive/support to industry for the development of new antimicrobial VMPs. The questionnaire related only to this aspect of the PRP. It was sent to the following interested parties: • AnimalhealthEurope • Association of Veterinary Consultants (AVC) • Bureau Européen des Unions de Consommateurs (BEUC) • COPA-COGECA • European Association for Veterinary Pharmacology & Toxicology (EAVPT) • European Group for Generic Veterinary Products (EGGVP) • Secretary General Fédération Européenne Des Emballeurs Et Distributeurs De Miel (F.E.E.D.M.) • Federation of Veterinarians of Europe (FVE)

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	Also, there are major, relevant concerns about advocating this 'Preliminary Risk Profiling' document for purposes of specifying conditions for the New Veterinary Regulations (NVR). The Preliminary Risk Profiling document is advocated for: 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 major, relevant concerns about using the document for these purposes include: ➢ The 'Preliminary Risk Profiling' document is not purpose-built for these needs specified above. The 'Preliminary Risk Profiling' does not fulfill the mandate in terms of design, methodology and scientific standards, particularly in relation to public health. For example, it states in the 'Preliminary Risk Profiling' document that "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." (Lines 173-175). Thus, the early hazard characterization was never designed to indicate which antimicrobials should NOT be intended for the VMPs and thus cannot be used for this part of the NVR. ➢ The 'Preliminary Risk Profiling' involves a questionnaire with	• Secretary General Groupement Pharmaceutique de l'Union Européenne (PGEU) • International Council on Animal Protection in Pharmaceutical Programs (ICAPPP). A response to the questionnaire was received from two of the organisations listed above. Subsequently, the draft PRP document has been published for open public consultation on the EMA website. As stated above, the approach for the PRP is based on the CVMP's draft GL on the Risk Assessment of Antimicrobial VMPs, which is based on the OIE (Terrestrial Animal Health Code, chapter 6.10) and Codex (CAC/GL 77-2011) methodologies. Account is also taken of the AMEG categorisation, which itself fully takes into consideration the WHO and OIE lists. The underlying methodology for the PRP is based on the CVMP's draft GL on the assessment of the risk to public health from antimicrobials VMPs EMA/CVMP/AWP/706442/2013. This document has been published twice for open consultation and is directly focused on risks to public health. The PRP methodology is separated into two sections. Section 3 relates to 'Use of the PRP in development of antimicrobial VMPs'. Section 4 relates to 'Use of the PRP in the context of the new Regulation on VMPs'. This section has been amended in response to a new mandate received from the

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	major input from the pharma industry. There is no mentioning in the 'Preliminary Risk Profiling' that respected groups involved in public health (e.g. WHO, FAO, EFFORT, OIE) were ever consulted. For example, it states in the 'Preliminary Risk Profiling' document that "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." (Lines 201-203). Thus, public health interests are not represented both in the initial consultation phase and overall design of the 'Preliminary Risk Profiling', which is not consistent with the mandate. For example, in section 3 of the 'Preliminary Risk Profiling' document under objectives of the questionnaire, it states "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)". There is no mention of seeking the views of public health interested organisations. ➢ The purposes stated for the 'Preliminary Risk Profiling' include: o "An aim of the **'Preliminary Risk Profile'** 1 (**PRP**) would be to encourage development by industry of new antimicrobial VMPs for use in animals, by increasing the predictability of a <u>positive regulatory outcome</u>." (Lines 217-218) o Increased regulatory predictability at early product	Commission regarding scientific advice relating to implementation of Regulation (EU) 2019/6 (the NVR). These comments are addressed above. Amended: '…predictability of ~~a positive~~ <u>the</u> regulatory outcome.'

1 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.

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	development stage. None of these stated purposes are specifically related to protection and preservation of public/human health and thus the 'Preliminary Risk Profiling' should not be used for specifying conditions for the NVR, including human-use only of antimicrobials. Since these are the stated aims of the document, then it is unclear as to how the One Health approach was ever considered. For example, it states in the 'Preliminary Risk Profiling' document that "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." (Lines 238-241). ➢ The 'Preliminary Risk Profiling' does not follow a recognizable scientific standard. For example, no recognized scientific published risk assessment/analysis standards are quoted/used as a template/model (e.g. *Codex Alimentarius, HACCP, Codex texts on foodborne Antimicrobial resistance - Codex Alimentarius*, OIE International Animal Health Code - Chapter 6.10, Quantitative Microbiological Risk Assessment (QMRA) model) for developing the 'Preliminary Risk Profiling'. Some of these codices follow the principles outlined in 'Preliminary Risk Profiling' (e.g. Hazard identification, Release assessment, Exposure assessment, Consequence assessment), and thus it is unclear as to why the 'Preliminary Risk Profiling' is not aligned with recognized/established scientific published risk assessment/analysis standards that were designed by groups focused on public health (WHO, FAO). In the mandate to the AMEG, it was specified that recent work/documents from WHO/OIE should be taken into account in the AMEG work, which does not appear to be the case at all with the 'Preliminary Risk Profiling' document.	In the answer to Question 3 from the Commission published in 2014, the AMEG concluded that 'authorisation of completely new classes of AM for use in animals could decrease the animal and public health risk due to AMR…' The PRP is based on a recommendation from that advice. The intention is to have a methodology for use at early stage development of new antimicrobial VMPs when information on dose regimen and indications/target pathogens would not be available. Please see the comments above.

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	➢ No outcome measures are stated for the individual parts of the risk assessment. For example, Codex texts on foodborne Antimicrobial resistance - *Codex Alimentarius* specifies each part of the risk assessment process to be summarized with a semi-quantifiable outcome measure (e.g. Negligible, Moderate, High). Typically, in a qualitative risk assessment, the probability of the population being exposed to the hazard is translated into a series of qualitative statements. The qualitative risk assessment requires expert opinions or other formalized, transparent and documented process to take the existing evidence and convert it into a measure of the probability of exposure. o Negligible (0) – Virtually no probability that exposure to the hazard can occur; o Moderate (1) – Some probability for exposure to occur; o High (2) – Significant probability for exposure to occur. The assignment of both a statement reflecting the exposure probability as well as a corresponding score is done to facilitate the process through which the exposure and hazard characterization will subsequently be combined. No clear direction is derived at the end of the process of the 'Preliminary Risk Profiling' if the antimicrobial substance should continue into an MA application or stop. No clear outcome measures are stated for each part of the risk assessment and thus it is unclear as to how the practical use of the document can lead to early hazard characterization.	Further reference can be made to the CVMP's draft GL on the assessment of the risk to public health from antimicrobials VMPs EMA/CVMP/AWP/706442/2013 regarding the scaling of risk indicators. Reference to this guideline to assist the assessment has been added (3.3.3). It is foreseen that the evaluation will be based on limited data, as outlined in section 3.3.2 and 3.3.3., and the outcomes will be similarly limited. Table 3 indicates that the aim is to give a high level estimate of the human health risk, to identify data gaps and potential risk management measures. It is not expected that a detailed qualitative RA will be possible at the PRP stage, and this is not included in the specified outcomes in section 3.3.4.
	➢ The 'Preliminary Risk Profiling' document has never been tested. No 'mock-up' scenarios are presented that identify if the questions/data requested are even realistic at early-stage development and whether the 'Preliminary Risk Profiling' leads to conclusions that are in the interests of animal and	

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	public health. Thus, it is unclear if this is a quality risk assessment that does not lead to under/over estimation of the risks identified.	
	There are several elements of Table 1 that are unclear: Hazard Characterisation: - It is unclear as to why the stated points of Hazard Characterisation were chosen and not others. For example, many other points under Hazard Characterisation are considered in the *Codex texts on foodborne Antimicrobial resistance - Codex Alimentarius* but not considered in the 'Preliminary Risk Profiling' document. It is unclear which specific points are relevant for companion animals versus food animals. - It is unclear as to why the AMEG categorization is only considered and not other categorisations (e.g. WHO, OIE). - Whether the new antimicrobial substance could select for multi-resistance (genes, plasmids or cassettes) is not considered and would be a clear hazard compared to those antimicrobial substances that do not select for multi-resistance. - It is not at all considered if the new antimicrobial substance is a WHO CIA or not. This directly relates to the benefit:risks assessment. - Use/s of the new antimicrobial in human medicine is not considered.	Please note, there is no heading 'Hazard Characterisation' in the table – the OIE methodology is used which includes separate hazard identification and consequence assessment. A footnote has been added referencing the CVMP Reflection paper on the risk of antimicrobial resistance transfer from companion animals EMA/CVMP/AWP/401740/2013, which includes discussion of relevant microbiological hazards. The AMEG categorization already gives consideration to the WHO and OIE lists. The occurrence of cross- and co-selection are taken into account. Selection of multi-resistant organisms has now been included. The importance of the AM in human medicine is considered in the consequence assessment.

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	- The mutant prevention concentration (MPC) and mutant selection window (MSW) are not considered at all. Release Assessment: - Unclear as to the definition of release assessment used in this document and difference between release versus exposure assessment. Our understanding of Release Assessment comes from the OIE International Animal Health Code that states the Release assessment is the description of biological pathways for release of hazard and estimation of its probability. Thus, it is unclear as to how understanding the use/indications, target animal/species is consistent with the definition of release assessment for each of the hazards identified in the hazard characterisation part of the table. No probability can be assessed under the points currently included for the release assessment. - In the *Codex texts on foodborne Antimicrobial resistance - Codex Alimentarius*, the same points listed for release assessment in the 'Preliminary Risk Profiling' document are under exposure assessment. This is more correct since exposure assessment = description of biological pathways necessary for exposure of humans / animals to the hazards necessary for exposure of humans / animals to the hazards released and estimation of its probability (OIE International Animal Health Code). Exposure Assessment: - Unclear as to the definition of exposure assessment used in this document. The potential exposure of humans to the resistant micro-organisms or resistance determinants released from a given antimicrobial use in animals should be listed in the exposure assessment, instead of expecting the applicant to list potential exposures. This provides	Detailed relevant information on the MPC and MSW may not be available at the stage of the PRP, which is intended to be a high level risk profiling. As outlined in section 3.3.3, the approach is 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 706442/2013). That document follows the OIE methodology as the 'release' step is particularly applicable when considering risk management measures that might be applied to VMPs. Understanding of target animal species and indications gives an indication of the extent of use of the product and hence the probability of 'release'. See above.

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	consistency between risk assessments and more clear direction for the applicant. - It is unclear as to why many other points under Exposure Assessment are considered in the *Codex texts on foodborne Antimicrobial resistance - Codex Alimentarius* but not considered in the 'Preliminary Risk Profiling' document. Consequence Assessment: - The consequence assessment is not clearly and logically connected to the other parts of the risk assessment.	Please note that OIE and Codex use different terminologies. It is not helpful to apply the OIE definition of 'exposure' to the Codex data requirements.
4	Our thanks for the opportunity to comment the document. The document is important part of guidance/actions that are necessary to preserve the efficacy of antimicrobials. It is noted that this is quite technical document and thus not easy to read. Therefore, quite many small technical comments is made for your consideration.	Thank you for your comments.
5	Overall, excellent approach to streamlining the process for assessing risk during the development of antimicrobial veterinary medicinal products. Canada supports efforts to streamline risk assessment processes and to make them "fit for purpose". The document would be improved if there was a specific section dedicated to describing in detail the 'Prescribing Cascade'; not just a footnote on page 3. For the use of the preliminary risk profile in the context of the new regulation on VMPs, there is some confusion in the tables provided	Thank you for your comments. This was not included previously as the EU audience was aware of the underlying principle of the cascade, and the new Regulation (EU) 2019/6 had not yet been adopted. Section 4 has been amended in response to a new mandate received from the Commission regarding scientific advice relating to implementation of Regulation (EU) 2019/6. A detailed discussion of the prescribing cascade does not now seem necessary in the revised document.

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	and how the information required would be applied to existing products or to new applications for marketing authorization. For example, for existing products, it would seem appropriate to use the column heading “substance/class+species+pharma form) as this information is already known. Hence, the other two columns may not be necessary?	This text is now deleted.
	About the term Preliminary Risk Profile: It is understood that this term was chosen in lieu of “early hazard identification” (line 175) to avoid confusion with Codex terminology. In the Codex context a risk profile is one of the first steps of a risk analysis, preceding a formal risk assessment (which includes formal hazard identification and hazard characterization). Using the term Preliminary Risk Profile might still be confused with Codex terminology and, due to the word preliminary, can be misunderstood to precede the risk profile as defined by Codex. Suggest an exploration of alternative terminology to avoid confusion.	New text has been added: *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’.*
	It is not only resistance in bacteria that are of concern, or indeed antimicrobials that are only aimed at treating bacterial infections, but also protozoa, fungi, etc. A suggestion is to use the term organism throughout the document.	Agreed. Amendment made: ‘Regulation (EU) 2019/6 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

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		requirements may not be fully applicable to other types of antimicrobial although the approach may be followed at high level'.
6	Les antimicrobiens utilisés chez les animaux de compagnie semblent inclus jusqu'à un certain point, mais le focus semble porter sur l'utilisation chez les animaux d'élevage. Or, pour différentes raisons (ex. profil des classes d'antimicrobiens utilisés, intimité avec les humains), les animaux de compagnie devraient faire l'objet de préoccupations au moins aussi marquées sinon plus que pour les animaux d'élevage. *Translation:* *Antimicrobials used in companion animals seem to be included to some extent, but the focus seems to be on the use in farm animals. However, for a variety of reasons (eg, antimicrobials profile used, intimacy with humans), companion animals should be at least as concerned as, even more than, livestock.*	It is agreed that the PRP would be equally of interest to companies developing products for companion animals. The PRP guidance is applicable to antimicrobial use in all domestic animal species. A footnote has been included to reference the CVMP Reflection paper on the risk of antimicrobial resistance transfer from companion animals EMA/CVMP/AWP/401740/2013, which provides further information on potential microbiological hazards for transfer of AMR from pet animals to humans.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 114	1	Comment: include also public health and food safety impact Proposed change (if any): … and any impact on animal health, welfare, **public health including food safety**, aquaculture and farming if…	Line 114 refers to the **'risk-risk' scenario**, which are the risks associated with not allowing use of an antimicrobial substance/VMP in animals/under the cascade. This specific line has now been deleted, but the comment is also relevant to Table 1. Produce from untreated diseased animals should not enter the food chain, but the scope of data has anyway been widened: '*Other impacts such as on aquaculture/farming if restrictions are placed on the proposed new treatment.'*
Lines 270-273	3	"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." Comment: It is unclear as to how involving these working parties is part of a One Health approach. For example, no working parties from CHMP are included or other groups dedicated to public health. It is unclear as to why consistency with the AMEG categorisation is the only need and not other international categorisation systems (e.g. WHO, OIE). The stakeholders participating in this 'Preliminary Risk Profiling' document indicated that "The possibility for involvement of expertise from a human medical background or	The AWP and AMEG include representatives from human, public and animal health backgrounds. The AMEG aims to maintain consistency with WHO and OIE where justified, but has considered AM usage specifically in the EU context and considers the importance of the substance to human and animal health. Any future EMA/CVMP collaboration with VetCAST is

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		collaboration with third countries was seen as a potential benefit." (Lines 260-261). It is further unclear as to why VETCAST or EUCAST would not be consulted.	primarily intended in regards to AST and setting of clinical breakpoints. CVMP has the possibility to liaise with CHMP if this is considered necessary. Also, where the need arises, the CVMP has the possibility to seek input from other relevant subject matter experts
Lines 274-275	3	"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. " Comment: If this is true then why is the 'Preliminary Risk Profiling' document not in-line with FDA Guideline #152?	The CVMP's Antimicrobials risk assessment guideline has been developed based on OIE and Codex, but also taking account of FDA guideline #152. Although these guidance documents are not fully aligned, and needs of animal and human medicine may differ between jurisdictions, this does not preclude future collaboration. Indeed, the concern raised (differences in regulatory approaches/requirements), could be raised in the context of any parallel scientific advice; yet, a number of these procedures have been concluded successfully.
line 87	4	Comment: - Consider to clarify the meaning of the sentence: OH needs to be considered – not promoted. Proposed change (if any): … ~~to promote~~ <u>in order to take into account</u> a One Health approach.	Amended: 'Provision could be made for consultation with CVMP working groups (AMEG, Antimicrobials Working Party - AWP) to ~~promote~~ **support** a One Health approach.
lines 233-235	4	Comment:	It is preferred to retain the feedback from the stakeholders.

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		- If understood right this is already part of the guidance how to carry out PRP, thus the first sentence seems unnecessary. - In the second sentence it is not clear what kind of expertise should be obtained from the collaboration with third countries. Maybe this could be clarified. Proposed change (if any): ~~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.	In relation to the second bullet, the stakeholder respondent did not provide further clarification therefore it will not be expanded further in the document. Recognising that AMR is ultimately a global problem, collaboration with third countries may facilitate knowledge exchange and help regulators come to a common position when it is scientifically justifiable
line 249	4	Comment: - Proposed change (if any): United Sates' FDA => United States' FDA	Amended. Thank you.
lines 300-301	4	Comment: - It is not clear if these two lines are part of the table to or part of the text. - If there is no specific reason to consider only livestock industry the term "livestock industry" should be replaced the terms "farming/aquaculture" which are used elsewhere in the document	These two lines are part of the text. Some changes have been made to the headings to clarify. This change has been made. The term 'farming/aquaculture' has greater consistency with the new Veterinary Medicines Regulation (EU) 2019/6.
line 307, Table 3	4	Comment: - In the middle column, 2nd last para the term "livestock	Amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		industry" should be replaced the terms "farming/aquaculture" which are used elsewhere in the document, unless all this is from the previous answer. It is not clear from the text. Proposed change (if any): … animal health and the ~~livestock industry~~ farming/aquaculture if restrictions ….	
line 314	4	Comment: - Official Journal of the European Union, 2019 could be referenced also here; not only in the summary	Amended.
line 346	4	Comment: - It seems that there are some words missing from the heading Proposed change (if any): 4.3.1. Scope of antimicrobial substances/classes that may be considered in the PRP	This text is now deleted.
line 354	4	Comment: - It is agreed that consideration of antimicrobials for which conditions should be placed on cascade use is important. Especially per oral group treatments could have marked influence on the resistance development.	Agreed. Please note that Section 4 has now been amended.
lines 369-371	4	Comment: - Abbreviation AM is used both in Table 1 and 4 but not explained anywhere? Could this be included in the table	The abbreviation has been included in the table heading, where required.

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		heading? Proposed change (if any): - AM = antimicrobial substance	
line 373, table 4	4	Comment: - It would help reader if complete words were used Proposed change (if any): - Heading of the 3rd column: Substance + animal species + pharmaceutical form	Amended where relevant.
line 380	4	Comment: - Explain blue text also in this table heading. - Should here be a reference to Table 2 (as in the heading of table 4 is to table 1)? Proposed change (if any): - The blue text below indicates the additional data required to those in Table 1	This text is now deleted.
Table 1 – Hazard Identification	5	Comment 1: The "Substance/class only" column for Hazard Identification states "Susceptible zoonotic or commensal bacterial spp.: *Campylobacter spp., Salmonella spp., E. coli, Enterococcus spp., Staphylococcus aureus".* Our question is whether the data to be provided here are from isolates from food animals on farm, healthy slaughtered animals, retail food, or humans? Comment 2: The subheading below **"Hazard Identification"** in	The key concern relates to transmission of AMR from an animal to a human host; therefore relevant antimicrobial resistance genes (ARGs) should preferably have been identified in organisms from animal (sick or healthy) sources. Identification of ARGs in environmental bacteria, possible food contaminants or human only sources can be regarded as supporting

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		column 1 reads “resistance to the AM in zoonotic bacterial pathogens or resistance genes in commensal organisms that may be transferred to human pathogenic bacteria”. This sounds like the only resistance genes that are of concern are those in commensal bacteria. Proposed change (if any): Wording change: Resistance to AM and/or resistance determinants in zoonotic pathogens and/or commensal organisms that may be transferred to humans or to organisms potentially pathogenic to humans.	information where provided. No change made. A cross-reference is made to the CVMP’s draft guideline on the assessment of the risk to public health from antimicrobial VMPs (EMA/CVMP/AWP 706442/2013) for further explanation. Accepted, with minor amendment.
Table 1 – Release assessment	5	Column 3 states ‘Exposure of gastrointestinal microbiota or skin/mucosal flora to active substance/metabolites’ Suggestion: Add the need for pharmacokinetic information so that excretion of potentially AMR inducing metabolites into the environment can also be assessed	It is agreed that excretion of AM and AMR into the environment is an important topic and CVMP has developed a reflection paper to discuss this issue (EMA/CVMP/ERA/632109/2014 – at consultation). No new data requirements are proposed at this time, as it is acknowledged that there is a need to build expertise in their evaluation in the regulatory context.
Table 1 – Consequence Assessment	5	Comment 1: For the “Substance/class only” column for the Consequence Assessment, it states “Extent of use of the AM substance/(sub)class in human medicine in the EU”. Our question is what does “extent of use” mean? Is this a quantity of use? Number of labelled products? Etc. If it is intended to mean quantity of use, how will the degree of appropriate/inappropriate use (in human medicine) be determined, and what will the impact of that be? Also, does a high level extent of use in humans generate more of a concern than a low level extent of use? For	More detailed guidance is available in the CVMP draft guideline on the risk assessment of antimicrobial VMPs (EMA/CVMP/AWP/706442/2013). A cross-reference is included, but detailed data are not expected at the stage of the PRP. Please refer to the CVMP’s risk assessment

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		products such as carbapenems in humans, there may be very low extent of use, but these are extremely critical drugs used as last resort. Comment 2: Consequence assessment column 2 states 'Importance of the antimicrobial in human medicine for treating the identified hazards(s) and severity of the disease'. It is not only resistant infections caused by the specific identified hazards that are of concern, but also infections caused by organisms that are resistant due to transfer of resistance determinants from the identified hazards. Also, it might be necessary to identify measures of severity (burden of illness measures)- are we looking at morbidity, mortality, frequency of treatment failures, duration of hospital stays, economic burdens, etc.? Proposed change (if any): Importance of the antimicrobial in human medicine for treating the infections caused by the identified hazard(s), or by organisms resistant due to resistant determinant transfer from the identified hazard(s), and severity of disease.	guideline for guidance on the interpretation of the data. Accepted. Amendment made. See also cross-reference CVMP's draft guideline on the risk assessment of antimicrobial VMPs
Table 1 – "Risk-risk scenario"	5	Comment: The table states "Impact on aquaculture/farming if restrictions are placed on the proposed new treatment". There would be no impacts if something that is currently not marketed is restricted correct? If the product is already being used in an off-label manner, then perhaps subsequent restrictions of the new licensed product might apply? Suggest to add text to clarify this.	Not fully supported. If there are no/limited treatments available for the disease, then the impact is an on-going loss to production or animal welfare, as opposed to its amelioration.
Table 2	5	Comment 1: In the "Component of the PRP" column, it states "tailored to species". We predict that this means 'animal species'	Accepted. Amendment made.

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		(and not bacterial species) given the types of data requested under release assessment and exposure assessment; adding 'animal' would improve clarity. Comment 2: Column 1, under 'Consequence': Similar to the above comment, it is not only the infection caused by the specific identified hazard that is of concern, but also infections caused by organisms that became resistant due to resistant determinant transfer from the identified hazard. Proposed change (if any): 'Importance in human medicine to treat infections caused by the identified hazard, or by organisms that are resistant due to resistant determinant transfer from the identified hazard'	As this is a schematic and a clearer outline of the consequence step is given in Table 1, the text has been abbreviated.
Lines 363-364 Table 4	5	The table does request information on "spectrum of activity in regards to important target animal pathogens" under the heading "Substance only (Reserved List and Cascade conditions)" – suggest this might be better placed under "Substance + target animal species (Cascade conditions)". This would be true of several other items related to animal exposure, importance of the antimicrobial to animal health, AMR risks to animal health, availability of alternate treatments for use in animals for the disease(s) in question etc.	Section 4 has been amended in response to a new mandate received from the Commission regarding scientific advice relating to implementation of Regulation EU 2019/6; therefore table 4 is now deleted.
Line 234-235	5	About the statement, 'involvement of expertise from a human medical background was seen as a potential benefit". The involvement of human medical expertise is crucial, not just a potential benefit. Assessing risk to public health with an integrated 'One Health' approach is impossible without involvement from expertise from human health experts, in addition to animal health	Agreed; this statement reflects the comment received from a stakeholder.

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		experts.	
Line 274	5	Are the target species referred to the animal or bacterial target species?	Amended: 'target animal species'.
461	6	Question 1 : un des éléments évalués sera le potentiel de transfert de la résistance aux antimicrobiens (RAM) des animaux vers les humains. Le transfert de résistance entre animaux et humains est un sujet complexe qui ne fait pas consensus dans la communauté scientifique. Comment ce potentiel sera mesuré mais surtout interprété en matière d'importance du risque que ce potentiel représente me semble être un enjeu de la proposition. **Il y a risque de menacer le développement de molécules en médecine vétérinaire si c'est interprété de manière très restrictive.** *Translation :* *Question 1: One of the elements evaluated will be the potential for transfer of antimicrobial resistance (AMR) from animals to humans. The transfer of resistance between animals and humans is a complex subject that does not reach consensus in the scientific community. How this potential transmission will be measured but especially interpreted in terms of the importance of the risk seems to me to be a challenge of the proposal.* ***There is a risk of threatening the development of molecules in veterinary medicine if it is interpreted in a very restrictive way.***	The comment is noted and it is acknowledged that estimating the risk for AMR transfer between animals and humans is complex. This topic is further addressed under TOR 1. It is noted in section 3.1.2 that a precautionary approach to the PRP would be a disincentive to product development. The outcomes are aimed at identifying areas of concern and data gaps in the risk assessment that would need to be addressed in a future marketing authorisation application, as well as options for risk management measures.
483	6	Question3 : parmi les risques non mentionnés du processus (page 22), malgré la prétention que le processus permettra d'augmenter le potentiel de « prédictivité » et que cela sera suffisant pour	

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		susciter l'intérêt de développer de nouvelles molécules en médecine vétérinaire : si on compare avec les enjeux du processus d'approbation au Canada, il est plutôt probable que le processus va au contraire décourager les compagnies pharmaceutiques, puisqu'une grande partie de la recherche et de ses coûts surviendront AVANT ce processus préliminaire d'évaluation du risque. On risque donc de décourager la recherche de nouvelles molécules pouvant être utilisées pour les animaux, en particulier pour les espèces mineures. On voit, par exemple, à la page 21, que le résultat pourrait être de limiter à certaines espèces seulement l'autorisation d'utilisation, et ce, sur la base des données fournies par le fabricant, qui risque de ne fournir des données que pour ses marchés principaux. Un des dangers de la proposition européenne est lié au fait que la masse critique d'animaux des espèces dites mineures est plus élevée en Union européenne qu'au Canada. Les compagnies pharmaceutiques vont donc faire homologuer certains produits en UE mais pas au Canada (ils comptent sur la possibilité pour les médecins vétérinaires ici de faire des prescriptions dites hors homologation sur la base des informations internationales). Si le processus s'alourdit en UE, il y a aussi un réel danger que les nouveaux produits pour espèces mineures ne soient plus soumis en UE et donc encore moins au Canada, en l'absence des données probantes issues du processus d'homologation européen. *Translation :* *Question3: Among the risks not mentioned in the process (page 22), despite the claim that the process will increase the potential*	

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		for "predictivity" and that this will be sufficient to generate the interest of developing new molecules in veterinary medicine compared with the issues in the approval process in Canada, it is rather likely that the process will deter pharmaceutical companies since much of the research and its costs will occur BEFORE this preliminary risk assessment process. It is therefore likely to discourage the search for new molecules that can be used for animals, especially for minor species. For example, it can be seen on page 21 that the result could be to limit the authorization of use to certain species only, and this, on the basis of the data provided by the manufacturer, which may provide data only for its main markets.	Industry had the opportunity to comment on the PRP via a questionnaire and the process has been largely supported.
		One of the dangers of the European proposal is related to the fact that the critical mass of animals of so-called minor species is higher in the European Union than in Canada. Pharmaceutical companies will therefore register some products in the EU but not in Canada (they are counting on the possibility for veterinary doctors here to make off-label prescriptions based on international information). If the process grows in the EU, there is also a real danger that new products for minor species will no longer be submitted in the EU and therefore even less so in Canada, in the absence of evidence from the European approval process.	If a risk assessment has been found to be acceptable for use of a medicine in a major species in the EU, then it is unusual that its use in a minor species would be restricted unless there is a specific risk associated with use in that species.