20 January 2021
EMA/CVMP/517722/2020
Committee for Medicinal Products for Veterinary Use

Overview of comments received on 'CVMP strategy on antimicrobials 2021-2025' (EMA/CVMP/179874/2020)

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

Stakeholder no.	Name of organisation or individual
1	Diagnostics for Animals
2	Société Nationale des Groupements Techniques Vétérinaires (SNGTV)
3	European Federation for Pharmaceutical Sciences (EUFEPS) – EUFEPS Network on Veterinary Medicines
4	Federation of Veterinarians of Europe (FVE)
5	European Association of Chemical Distributors (Fecc)
6	AnimalHealthEurope (AHE)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Diagnostics for Animals is the representative Federation of the Veterinary Diagnostic Industry in Europe. It represents almost 90% of the companies operating on this market. 28 members, including 27 companies, are members in 2020. All are accredited by quality systems (ISO 9001 at least). A database on our website https://diagnosticsforanimals.com/ presents more than 1700 diagnostic tests available. Diagnostics for Animals participates in several committees: - European Commission AHAC - Discontools - Epruma - Star Idaz We have been informed of the recent "CVMP strategy on antimicrobials 2021-2025 (EMA/CVMP/179874/2020)" which has been published for a 3-month public consultation. One proposal is to develop a reflection paper on availability and characteristics of diagnostic tests and to contribute to the development of "clinical breakpoint". Our Federation would be very interested to bring its contribution. We propose you to put at your disposal our competence and our knowledge in order to help you in this mission.	Your interest in this important topic is appreciated. The sharing of your expertise as an interested party during the development of the reflection paper will be welcome.

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2	We appreciate the stated desire for harmonization both on the comparison of sales or usage statistics, as well as on the harmonization of SPC which today leads to very different practices between European countries. Practitioners are worried to see the list of critical antibiotics increasing each year with real therapeutic difficulties. Putting as an objective to regularly review this classification with possible "backtracking" depending on the evolution of the results of antimicrobial resistance gives some hope. We welcome the desire to improve exchanges with veterinary associations. However, we have identified a lack in this document: cooperation with human health should be improved to identify the most risky transmission routes from animals to humans in order to develop targeting actions. Banning or restricting the use of antibiotics in animal health cannot be the only solution to fight AMR.	Thank you for drawing attention to these issues from the practitioner's perspective. CVMP is pleased to receive comments on its strategy from veterinary associations. It is agreed that a One Health approach should be taken to AMR. The 'JIACRA' reports[1] analyse data from EU-wide monitoring networks to identify the potential relationship between antimicrobial consumption (AMC) in humans and animals and AMR. In the JIACRA II report, this analysis was refined to look for associations at species level, based on estimated AMC in pigs and poultry. As more robust data are collected on AMC in different animal categories, as required under Article 57 of the Regulation (EU)2019/6, it is hoped that this can be used to improve the analysis and our knowledge of the transmission routes associated with highest risk. This will enable more focused risk management measures, as clarified under Aim 5.

[1] https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/analysis-antimicrobial-consumption-resistance-jiacra-reports

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		It should also be noted that the AMEG's Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017), that may be used by policy makers and those developing treatment guidelines, was developed taking a One Health risk-based approach (see Aim 2 of the strategy).
3	The drafted "CVMP strategy on antimicrobials 2021-2025" is very well elaborated. We like to bring into consideration only a few more general comments: Caution should be exercised regarding the in silico-review of doses and withdrawal periods for (established) antibiotic products. For the time being, there is only limited experience with using such approaches. A definition of the terms „alternative" or "alternative methods/medicine" might help to avoid misunderstanding of what is meant. "Alternative" may be understood as to comprise also non-scientific methods and approaches.	Thank you for your comments. The CVMP notes the concerns raised in regard to modelling methods used for extrapolation of withdrawal periods. According to CVMP's reflection paper on dose review and adjustment (EMA/CVMP/849775/2017), this approach is intended only in the context of established veterinary antibiotics, where there is evidence that the current dose regimen is no longer up-to-date and the alternative might be the loss of availability of these products on the market. The adopted reflection paper provides general principles and it is acknowledged that as the science evolves, further changes to the proposed methodologies may be possible. The methodology makes use of worst-case estimations and addition of safety spans to compensate for uncertainties. The limitations of the methodology are presented in section 7 of the reflection paper. For this strategy document, where the term 'alternative' has been used in the context of the methodology for the environmental risk assessment, this has been revised to 'alternative scientific methodologies'. A working definition has been included for 'alternatives to antimicrobials', as referred to under Aim 4.

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	The importance of veterinary dispensaries/veterinary practice vehicles should be (at least) referred to, as proper storage and transport medicinal products (as well as the other usage advices of the SPCs) is mandatory	CVMP agrees that proper storage of veterinary medicines is important, but since this applies to all VMPs, and not just antimicrobials, it is preferred not to mention this matter in this strategy in case it is implied that it applies to antimicrobials in isolation.
4	FVE welcomes CVMP Strategy on antimicrobials 2021-2025. We very much welcome the CVMP mission statement, however suggest to include the environmental aspect. As recognised in the mission, it is very important to balance the risk to public health that could arise from the use of antimicrobials in animals, against the need to protect animal health and welfare. Our main feedbacks are: - Animal welfare is missing in the entire Strategy - The Strategy defines an ambitious program. Prioritisation and a timeline might be worthwhile additions. - A reference to the Farm to Fork Strategy adopted in May and its goals in respect to antimicrobials should to be included.	Thank you for your comments. Accepted. Amendment made: 'minimising the risks to animals, humans and the environment.' Antimicrobials are used to maintain animal health, which consequently impacts on animal welfare. An amendment has been made to Aim 2 ('to protect animal health and welfare') and in Aim 3, in relation to maintain established antimicrobial VMPs on the market to support animal health and welfare. The prioritisation and timeline for CVMP's proposed actions on AMR are included in the CVMP work plan, updated annually. This is preferred as it allows greater flexibility for review, as compared with this 5-year strategy document. The following text has been added (Aim 5): 'The new legislative provisions on sales data collection will also support the commitment in the Farm-to-Fork strategy[2] of the 'EU Green Deal' to reduce the sales of antimicrobials for

[2] https://ec.europa.eu/food/farm2fork_en

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	- We understand and agree that Regulation 2019/6 was used as reference for the definition of antimicrobials. However, resistance against antiparasitic products is also a growing problem and therefore we see a need for an additional strategy to cover aspects related to the use of antiparacsitics as well. - We strongly support the need for the development of clinical breakpoints and values. - Lot of focus is being put on the risk assessment, but it would be preferable to consider more the risk mitigation measures e. g. in Aim 1 and Aim 2. More focus could also be put on the aspect of route of administration.	farmed animals and aquaculture by 50% by 2030'. Comment noted for future consideration. Noted (Aim 5). The CVMP has an important role in regard to both risk assessment and risk management, for which several actions are proposed: Aim 1 includes an action to consider guidance in respect to prophylactic use of antimicrobials in accordance with Article 107(3). CVMP will also provide advice in relation to restrictions on cascade use as required by Article 107(6) – see Aim 5. The CVMP intends to publish the revised Guideline on the SPC for Antimicrobial VMPs to coincide with the application of Regulation (EU)2019/6; the related action under Aim 5 has been amended to emphasise that CVMP will continue to ensure that the advice provided in SPCs includes specific risk management warnings to limit the development of AMR. The revised AMEG Categorisation report (EMA/CVMP/CHMP/682198/2017) has already included a listing of preferred routes of administration; which has been communicated via an infographic. Please note that AMEG considered that further research is needed in this respect.

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	- It would be good to detail the role that UPD can play in facilitating Aim 3 and Aim 5 e.g. to open up the possibility for more prudent and responsible use, by allowing, for example, the use of a lower category antibiotic from another EU country, or the use of alternatives to antibiotics.	The role of the Union database to facilitate cascade prescribing has been noted under Aim 5.
	- There is an increasing trend to restrict antibiotics allowed to be used in animals, while several indications could be easily controlled via a narrow spectrum antibiotic available in another country or simply by increasing the dose of a currently available narrow spectrum antibiotic in the same country. Nevetherless, none of these scientifically acceptable options is currently not allowed. In other cases, however, there are indications, where a shorter duration of treatment is proven to be as effective as the one indicated in the PIL. Pharmaceutical companies are hesitant to change the SPC and the used parameters to cover such issues, seen the amount of resources needed to do so. In addition, new treatment concepts (like the Mutant Prevention Concentration theory) are currently not allowed/available in practice. It would be great if the CVMP would really promote new opportunities for treatment with narrow spectrum antibiotics or lower dosage/duration – when possible and the use of other alternative options to facilitate responsible use of antibiotics in animals, rather than continuing to restrict the available options causing more problems in animal health and welfare.	An important part of CVMP's role in the regulation of VMPs is to ensure that the target species, indications, dosing regimens and safety warnings included in a product's SPC are evidence-based. The Strategy includes several actions that are aimed at encouraging development of existing and new antimicrobial VMPs: • Recommendations of the CVMP's reflection paper on dose review and adjustment for established antibiotics will be taken forwards (Aim 3). • The CVMP will continue to provide regulatory and scientific advice on the development of new and existing antimicrobial VMPs e.g. through scientific advice (Aim 4). • CVMP will investigate the barriers preventing access to, and use of, certain category D antibiotics in veterinary medicine (Aim 3).
	- FVE welcomes that a reflection will be made upon the use of currently available tests and novel rapid diagnostic testing	Comments noted.

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	methods as a means to improve rational prescribing. Practical implications, such as how easy it is to take a sample, how many animals to sample, time it takes to get the results, costs of testing and animal owners willingness to pay for that, availabilitye of tests in the different parts of Europe, should also be taken into account. It is nice to see in the annex an overview of the activities undertaken by CVMP in 2016-2020 (EMA/CVMP, 2016a). It is noted that some actions are still ongoing. It would be good to check at a certain moment the effectiveness, relevance, coherence and importance of the different actions taken, based on an assessment by the different regulatory authorities and stakeholders, in order to facilitate future prioritisation.	It is agreed that this would be a useful activity for the European Medicines Agencies Network and/or other stakeholders to take forwards.
6	AnimalhealthEurope welcomes the opportunity to comment on this draft strategy. We welcome the transparency and willingness to cooperate with stakeholders as expressed in the document. However, it is not possible to get any sense of relative priorities or timings for the many different activities identified, some of which featured in the last strategy without any evidence, as yet, that they have progressed. It would be very helpful if information on priorities and approximate timings could be included in the strategy document.	The Annex to the Strategy includes a status report of the extensive activities undertaken by CVMP on antimicrobials from 2016 to 2020. This includes an update against the actions included in the strategy. It can be seen that almost all actions were completed, are close to completion or are on-going by their nature. Two actions were de-prioritised. The CVMP has had additional tasks in 2019 to 2020 relating to mandates to provide scientific advice to the Commission in relation to the implementation of Regulation (EU)2019/6. Together with the impact of the Covid pandemic on business-continuity, this has resulted in a delay to timelines for other tasks. The prioritisation and timeline for CVMP's proposed actions on AMR are included in the CVMP work plan, updated

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		annually. This is preferred as it allows greater flexibility for review, as compared to this 5-year strategy document.
	We feel that the review of the AMEG categorisation assessment is too narrow and should include additional aspects such as the route of administration.	Regarding review of the AMEG categorisation (route of administration), please see response to comment on Line 63.
	Furthermore, we would welcome CVMP's recognition of vaccines as an effective measure that could be applied to reduce the need for antimicrobials, and from that conclusion would put extra effort in minimizing regulatory hurdles for (novel) vaccination technology	Vaccines are included within the scope of the CVMP's Reflection paper on promoting the alternatives to antimicrobials in the EU (EMA/CVMP/461776/2017); however, the CVMP has established a specific ad-hoc expert group on vaccine availability (CADVVA) responsible for implementing CVMP's actions in this area, which are therefore now not included in the direct scope of the antimicrobials strategy.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
24-26	4	Comment: In the introduction, the effect of AMR on human health is mentioned, but the effect on the health and welfare of animals is missing. Please add. Proposed change: Please add a sentence on the effect of AMR on animal health and welfare.	An additional reference has been added to note that there are also consequences for animal health and welfare and food production, although these have been less well defined (Bengtsson and Greko, 2014). Further emphasis has been placed on the need for a One Health approach to address AMR.
45	4	Comment: add the environmental aspect in the mission Proposed change: 'The CVMP's mission is to ensure the availability of effective antimicrobial medicines for the treatment of infectious diseases of animals while, at the same time, minimising the risks to animals, humans or the environment arising from their use.'	Accepted. Amendment made.
53	6	Comment: It would be anticipated that risk assessment would be done prior to risk management. However, it is unclear what methods are to be used for the risk assessment. Would CVMP GL 644 remain the model to follow? Proposed Change: Please specify the risk assessment will be prior to any risk management steps proposed and which risk assessment model sponsors/CVMP should follow.	Data requirements in regard to antimicrobial resistance risk assessment will be laid out in Annex II to Regulation (EU) 2019/6. In relation to the AMR risk to public health, guidance is provided in VICH GL 27 and it is anticipated that the CVMP's Guideline on the assessment of the risk to public health from AMR due to the use of an antimicrobial VMP in food-producing animals (EMA/CVMP/AWP/706442/2013 draft) will be adopted in April 2021. In relation to the AMR risk to target animal species, guidance on the data to be provided is presented in the Guideline for the demonstration

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			of efficacy for VMPs containing antimicrobial substances (EMA/CVMP/627/2001). These guidance documents have not been referenced in the strategy from 2021 to 2025 as the focus is on CVMP's anticipated major activities during this period.
63	6	Comment: The AMEG's categorisation will be reviewed as required to take account of evolving patterns of AMR and antibiotic usage in human and veterinary medicine. Proposed change: Please consider adding route of administration to the scope of the review.	It was a recommendation of the AMEG's report on the *Categorisation of antibiotics in the EU* (2019) that the categorisation should be reviewed within 5 years in light of data collected annually in the EU mandatory AMR surveillance programme and on the basis of new evidence on changing patterns of antibiotic use (obtained annually through ESVAC and ESAC). Any proposal to review the listing for the route of administration would be dependent on the identification of a significant new body of evidence not available at the time of the drafting of the 2019 report.
58	4	Comment: add animal welfare Proposed change: 'Aim 2: To consider and advise on the risk to public health that could arise from the use of antimicrobials in animals, and to balance this against the need to protect animal health and welfare'	Accepted. Amendment made.
61	2	Comment / Proposed change : "as sources of antimicrobial resistance genes" may be replaced by "as sources of antimicrobial resistance mechanisms (genes, drugs interactions, etc…)".	Text amended: 'antimicrobial resistance determinants'.
63	4	Comment: add disease patterns.	It is preferred to leave the text so that it reflects the recommendation in the AMEG's report on Categorisation of antibiotics in the EU (EMA/CVMP/CHMP/682198/2017). It is

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		Proposed change: 'The AMEG's categorisation will be reviewed as required to take account of evolving patterns of AMR, antibiotic usage and disease patterns in human and veterinary medicine.'	probable that relevant changes in disease patterns will also affect antibiotic usage.
64-72	6	Comment: Whereas we fully support the ongoing surveillance of susceptibility patterns of bacteria, we are concerned about the approach on dose revision and adjustment for established antimicrobials. Most antimicrobials belonging to the D-category are old molecules and were developed a long time ago and often no recent data have been generated. Therefore, changing the dose in these established products may trigger updates to the assessments to protect human and environmental safety requiring the generation of additional data that may prove uneconomic and therefore could lead to the removal of established products from the therapeutic arsenal. This challenge was addressed in the CVMP reflection paper on dose optimisation of established antibiotics from July 2018 (EMA/CVMP/849775/2017) where a modelling approach was examined as an alternative to the generation of new data for clinical, residue depletion, TAS and ERA. This alternative approach should be further explored to become a concrete option and a review of dose should only be	Please refer to the recommendations on publication of the adopted reflection paper (re-named Reflection paper on dose review and adjustment of established veterinary antibiotics in the context of SPC harmonisation, EMA/CVMP/849775/2017). The procedure for selecting candidate products for dose review is included in chapter 2 of the reflection paper, where it is noted that differences in dosing regimens, evidence of lack of efficacy and evidence of decreased susceptibility of target pathogens will be factors considered. No amendment to the existing text could be identified in the proposed change made by the interested party.

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		undertaken where there is evidence of a new risk that would impact the benefit/risk balance. Proposed Change: Aim 3: To maintain the effectiveness of antimicrobial substances that are already authorised in veterinary medicinal products by monitoring and analysing their sales and usage, encouraging surveillance for changes in susceptibility of target pathogens and zoonotic bacteria, and subsequently reviewing the authorisation of substances and/or products, especially when there is evidence that there may be a related change in the benefit-risk of the authorisation.	
64 -68 & 201-203	2	Comment: Sales and usage are not a way to maintain the effectiveness of antimicrobial substances. Knowledge of dose, way of administration and treatment duration in real life is more relevant! To that effect, review and adjustment of old established veterinary antimicrobials are essentials	Accepted. The text relating to monitoring of antimicrobial sales and use has been moved to Aim 5 (Responsible Use).
66	4	Comment: Text mentions 'encouraging surveillance for changes in susceptibility of target pathogens and zoonotic bacteria,'. Will commensal bacteria also be included? Proposed change: -	Aim 3 relates to maintaining the *effectiveness* of antimicrobial VMPs. In this sense it is the susceptibility of target pathogens, which may include some zoonotic pathogens, that is relevant. Reference to zoonotic bacteria has been deleted in case of confusion. Monitoring of commensal bacteria is of relevance to the public health AMR risk and is conducted as required by Directive 2003/99/EC.

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66	6	Comment: Target pathogen susceptibility – Are EMA/CVMP proposing initiating a target pathogen monitoring program? Industry already has a robust target pathogen monitoring program under the umbrella of CEESA, the VetPath program. It is unclear why a new program would be needed for ongoing target pathogen monitoring. Additionally, there is ample published literature on target pathogen monitoring, would that data not be enough to look at trends? Proposed Change: Please consider referencing the CEESA VetPath program	The EU One Health Action Plan against AMR commits to identify and assess resistant bacteria that cause transmissible diseases in animals and, if necessary, to develop harmonised rules for their surveillance. In the framework of the Animal Health Law (Regulation (EU) 2016/429), the Commission has mandated EFSA to provide a scientific opinion on this point, potentially in collaboration with EMA/CVMP. In addition, EU-JAMRAI has proposed a public European surveillance network for AMR in target animal pathogens (EARS-Vet), similar to the EARS-Net programme on the human side. CEESA VetPath data are not publicly available, as far as we are aware. Further, CVMP proposes to provide guidance on the needs for post-authorisation studies that might be required in accordance with Article 36(2) of Regulation (EU)2019/6 in relation to potential development of AMR and maintaining a positive benefit-risk for antimicrobial VMPs. Hence it can be seen that under Aim 3, CVMP proposes to support actions encouraging the surveillance of target pathogen susceptibility.
67	4	Comment: remove the word 'especially' Proposed change (if any):. … and subsequently, reviewing the authorisation of substances and/or	Accepted. Change made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products, ~~especially~~ when there is evidence that there may be a related change in the benefit-risk of the authorisation.	
70	4	Comments: add animal categories Proposed change: 'CVMP will provide support to ESVAC in its preparations to receive data on sales and use of antimicrobials by animal species and animal categories, …'	Accepted. Amended: animal species/categories.
73-79	6	Comment: The scope of alternatives to antimicrobials has to be more widely defined. Alternatives to antimicrobials can be assessed and associated with ambitious claims since this would trigger more rapidly the change of veterinary practices systematically focused on the use of antimicrobials in the case of infectious disease. This needs to be promoted and supported by regulatory bodies through corresponding scientific guidance. Alternatives should be seen as a wide panel of options and not only as direct replacement of antimicrobials treatment to treat infections. In order to have these alternatives available it is necessary that the appropriate regulatory framework is set where the contribution to reduce the use of	Please refer to the CVMP's Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU (EMA/CVMP/461776/2017). These issues have been discussed with interested parties in the context of EMA's Regulatory Science Strategy to 2025. Please see the text and CVMP's proposed action in relation to this point in the detailed section of the strategy under Aim 4. CVMP intends to collaborate with other EU Agencies (EFSA, ECHA) on the classification and regulatory framework for alternatives to antimicrobials and to develop guidance, as appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		antibiotics is recognised as a benefit when evaluating these alternatives. The overall benefit for animal, environmental and public health should be taken into account to encourage durable changes. In this context, when developing alternatives, non-traditional endpoints should be considered and therefore guidelines should be adapted to take into account these new endpoints. Additionally the assessors approach to these new options / alternatives when evaluating their overall benefit / risk balance may need to evolve.	
75-77 & 243-248	2	**Comment**: Development of ATAm is one way to fight against AMR, but research for solutions limiting the release of antibiotics into the environment of treated animals should be encouraged **Proposed change**: In CVMP's proposed actions, one action must be added : development of antimicrobial chlelators and/or antimicrobial inactivators active in terminal gut of animals	Thank you for your advice. The CVMP's draft reflection paper on AMR in the environment (EMA/CVMP/ERA/632109/2014) considers risk management measures to reduce the input of veterinary antibiotics and resistance genes to the environment; although use of chelators and inactivators is not specifically mentioned. In addition, the paper advises of several knowledge gaps that hinder the AMR environmental risk assessment and where further research would be needed. The types of products mentioned may fall into the category of 'borderline products' for which the regulatory framework is to be developed. In the interim, CVMP is open to provide regulatory guidance on potential products through the Innovations Task Force. (See Aim 4).
78	2	**Comment**: Responsible use of antimicrobials is to use them in accordance with updated knowledge;	Not accepted. The proposed amendment could suggest that MAs at the time of initial authorisation are not adequate.

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		unfortunately, Marketing authorisations become obsolete after years for some products. Updating (dose regimen mainly, and withdrawal time) should be an obligation: SPC of many products should be updated ! **Proposed change**: the sentence could be "To support the responsible use of antimicrobial both in accordance with updated Marketing Authorisations...".	Legal provisions for referral procedures are in place to enable review of the benefit-risk and SPC for veterinary medicines on the identification of a potential serious risk. CVMP has conducted several of these procedures for antimicrobial VMPs in recent years (Annex to the strategy) and the strategy also includes actions to take forwards the recommendations from the (re-named) reflection paper on dose review and adjustment of established antibiotics (EMA/CVMP/849775/2017) and to support CMDv in the SPC harmonisation project (Aim 3).
81	4	Comment: For several species, indications, the cascade is the only option available to treat an animal with an antibiotic. Restrictions should only be put on certain antibiotic classes or for certain species, otherwise, this could severely endanger animal health and welfare. Proposed change: Scientific advice will be provided on the implementation of the new legislation pertaining to restrictions on the use of certain antibiotic classes under the cascade.	Accepted. The text has been amended 'certain antimicrobials'. This is further clarified in the detailed text under Aim 5.
83	4	Comment: Aim 6 – would be good to add a reference to the impact on animal health and welfare Proposed change: refer to impact on animal health and welfare	Amendments have been made (Aims 2 and 3) to include references to the impacts on animal welfare. Aim 6 is focused on collaboration with human and animal health organisations at EU and international level and we do not see a need for the additional text here as health and welfare are closely linked.

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88	6	Comment: Actions: CVMP will continue its engagement with its diverse stakeholders and to collaborate with colleagues in EU agencies and international regulatory bodies in developing guidance and advice on antimicrobial-related issues. Proposed change: please amend to "….. developing science based guidance and advice….."	Accepted. Amended as requested.
97	4	Comment: 'Aim 1. Provide opinions to support the authorisation of effective antimicrobial VMPs with measures ensuring safe and sustainable use'. What is exactly meant by "sustainable use"? Proposed change: please explain sustainable use.	'Sustainable' is used in line with the ordinary dictionary definition. The discussion under Aim 1 highlights measures and actions aimed at limiting the development of antimicrobial resistance so that the effective use of antimicrobials can be prolonged.
111-115	6	Comment: It is welcomed that guidelines will be updated in line with the New Veterinary Regulation. As per article 107 of Regulation (EU) 2019/6 "Antimicrobial medicinal products shall be used for metaphylaxis only when the risk of spread of an infection or of an infectious disease in the group of animals is high and where no other appropriate alternatives are available. Member States may provide guidance regarding such other appropriate alternatives and shall actively support the development and application of guidelines which promote the understanding of risk factors associated	This specific activity is not included within the CVMP's proposed actions as the Regulation states that this guidance may be provided by Member States.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with metaphylaxis and include criteria for its initiation". It is expected that future CVMP guidelines will address clarity on what is considered as "alternatives" and inclusion criteria to better define cases where metaphylaxis can or cannot be applied.	
120	6	Comment: Aim 2. Advise on the risk to public health of the use of veterinary antimicrobials and balance it against the need to protect animal health Proposed change: As was requested by the EU commission in the initial mandate given to AMEG for the categorisation review, Route of administration should be taken into account as can play a significant role in the development of AMR. AMEG recognised the impact of route of administration in the last review of the categorisation, though did not act upon it. Therefore, a new review of the categorisation should definitely include the route of administration.	Please see the response to the comment in Line 63. To note the following text from the AMEG Categorisation report (EMA/CVMP/CHMP/682198/2017): *Given that antimicrobials in each (sub)class are available in a number of different formulations and for administration by different routes, the AMEG chose not to include the route of administration as an additional criterion for the categorisation. It was the view of the group that to consider the relative AMR risk for all the different formulation/antimicrobial class combinations within the categorisation would be highly complex and difficult to evidence. Nevertheless, when factoring AMR risk into prescribing decisions, the aim should be to use the list above together with the AMEG Categorisation to select both the formulation/route of administration and class that will have the least impact on the selection of AMR. It is also acknowledged that these choices should be made taking note of the Summary of Product Characteristic for each given product.*
126	4	Comment: What is meant with 'alternative antibiotics'? Does it refer to the CVMP paper on	Please refer to criterion 4 for the AMEG Categorisation (EMA/CVMP/CHMP/682198/2017).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		alternatives to antibiotics or the O'Neill report mentioned inline 218? As commented in our response to that paper, most products which are considered as alternatives to antibiotics are not real alternatives. Most stimulate the immune response or have a preventive effect, while only a few of them have a direct curative effect. Proposed change (if any): please define 'alternative antibiotics' and include some examples	The text has been amended: 'the availability of alternative antibiotic treatment options for important diseases in veterinary medicine'.
140	4	Comments: What is meant with 'non-antibiotic antimicrobials'? Does it mean antivirals or anti-fungals? We should be careful with promoting the use of new substances until we are sure that they are not contributing to the problem, e.g. leading also to resistance, and that their use is science- and evidence-based without unforeseen negative consequences. Proposed change (if any): please explain what is meant with 'non-antibiotic antimicrobials' and include some examples	The definition of 'antimicrobial' provided in Regulation (EU) 2019/6 is cited in the Introduction: 'An antimicrobial is any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals'. 'Non-antibiotic antimicrobials' include antivirals, antifungals and anti-protozoals'. This has been explained in the text.
141	6	Comment: For the sake of clarity, it would be helpful to have a definition or examples of what is considered as non-antibiotic antimicrobials.	The definition of 'antimicrobial' provided in Regulation (EU) 2019/6 is cited in the Introduction: 'An antimicrobial is any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			'Non-antibiotic antimicrobials' include antivirals, antifungals and anti-protozoals'. This has been explained in the text.
158 & 253	4	Comment: In aim 3 and 5, please insert a reference on how the UPD can facilitate the availability and support veterinarians in responsible prescribing Proposed change (if any): please add a reference to the role of UPD Comment: In aim 3, the 3 yearly JIACRA report continuation is mentioned. The JIACRA report is highly welcome. However, it is recognised that this report makes use of data collected by different surveillance/monitoring systems with different aims and primary purposes in each sector. The integrated analysis of such data is inherently hindered by this bias. The availability of more detailed and comprehensive data would increase the scope of the analyses that can be performed and improve the robustness of the outputs. We suggest that CVMP also adds an action together with ECDC and EFSA to work towards a more coherent methodology of collecting data for the JIACRA report which will facilitate the interpretation and analysis of the results. Proposed change: add an action for CVMP together with ECDC and EFSA to work towards a more coherent methodology of collecting and interpreting data for the JIACRA report.	An addition has been made to the text under Aim 5, as follows: 'The updated AMEG categorisation is a useful tool for those preparing such guidelines or when prescribing under the cascade, which will also be facilitated by access to the Union Product Database.' JIACRA makes use of data from five EU-wide surveillance systems, without the burden of creating new systems. The JIACRA II report discusses the strengths and limitations of these systems and the on-going actions being taken to improve them in the context of their primary purposes. The report already notes that 'The availability of more detailed and comprehensive data would increase the scope of the analyses that can be performed and improve the robustness of the outputs'. In this respect, the JIACRA report itself makes several recommendations in its Overall Conclusions. However, CVMP supports that foremost the surveillance/monitoring systems should be refined according to their specific individual functions. The legal basis for cooperation of the EMA, EFSA and ECDC in the publication of the JIACRA report is laid out in Regulation (EU)2019/5. As noted under Aim 5, Regulation (EU)2019/6 introduces requirements for harmonised collection of antimicrobial sales and use data at animal species/category level. It is expected that CVMP/ESVAC will be closely involved with the implementation of these new

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			requirements – CVMP has already provided scientific advice in relation to the associated implementing and delegated acts. It is also noted in the strategy that further consideration is needed on the methodology for analysis of these data and that EMA/CVMP will continue to support JIACRA. No Amendment proposed.
3 & 210	4	Comment: ' CVMP will also investigate the barriers preventing access to, and use of, certain Category D antibiotics that could reduce the use of critically important antimicrobials in animals.' This is very welcome and urgently needed. However, should be accessible to all lower category antibiotics. Sometimes only a Cat B is available, then Cat C would also be beneficial Proposed change (if any): change to 'CVMP will also investigate the barriers preventing access to, and use of, certain Category C or D antibiotics that could reduce the use of critically important antimicrobials in animals'.	This action relates primarily to reports of lack of access in some members states to e.g. narrow spectrum penicillins to treat any species and aminopenicillins without beta lactamase inhibitors to treat pet animals. CVMP considers that the issue relates primarily to certain Cat D substances.
197	4	Comment: It is important, that actions should be aimed at keeping the benefit-risk relation positive. Unnecessary re-assessment with additional studies should be avoided as they will impose a high burden and may put products at risk of being taken out of the market. Any decision on re-assement with additional studies should be science- and evidence-based and avoid the resk to lead to a reduced availability of	Your comment will be taken into account when this action is taken forwards.

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		different classes of antimicrobials for the veterinary treatment.	
204-210	6	Comment: According to article 70 of Reg EU 2019/6, the MAH shall support the proposed harmonised SPC with existing data. As underlined in a previous comment, established antimicrobials are often old molecules for which recent data are not available and may not be sufficient to review the dose regimen. Therefore, alternative approaches should be considered as developed in the CVMP reflection paper on dose optimisation of established veterinary antibiotics in the context of SPC harmonisation. It is therefore essential that agreement on an alternative approach(es) is reached before setting priorities. It is feared that without a clear pathway, harmonisation of established veterinary antibiotics may prove resource heavy for both the regulators and industry and have a negative impact on the availability of medicines.	Concerns noted, however the SPC harmonisation will be the responsibility of the CMDv, not the EMA/CVMP, and is regarded as a separate exercise. Nevertheless, please refer to the recommendations on publication of the adopted reflection paper (re-named Reflection paper on dose review and adjustment of established veterinary antibiotics in the context of SPC harmonisation) (EMA/CVMP/849775/2017).
210	5	Comment: Add proposed change (sentence) on the last sentence Proposed change (if any): The CVMP should also ensure and assess that the Good Distribution Practices are maintained for Category D antibiotics.	Not accepted. The implementation of GDP measures does not fall within the remit of the CVMP; although we agree it is important to maintain accessibility and correct distribution of Category D antibiotics.

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243	4	Comment: While it is not further detailed what ATA will be, it would be good to emphasize that measures preventing disease and thus reducing the need for treatment are important. In saying this, vaccines definitely play a role to prevent diseases. They are well regulated, contrary to many other ATAs. Re vaccines, it is also important to allow and facilitate the use of products available in other member states, in case they are not available for use in the country of origin. Another aspect around ATAs is that many products are on the market as feed additives or just as products without authorisation to add to the feed. It would be good to have a clear regulation for the different types of products and more investment in research, such as to show that these products are really effective and pose no harm. Proposed change (if any): Add a sentence on the use of vaccines and one on regulation of ATAs (feed additive, VMPs without authorisation)	Please refer to the CVMP's Reflection paper on promoting the authorisation of alternatives to antimicrobials in the EU (EMA/CVMP/461776/2017). An action is already included under Aim 4: 'The CVMP will collaborate with other EU Agencies (EFSA, ECHA) on the classification and regulation of alternatives to antimicrobials (ATAm) including technologies to reduce AMR risk. Further guidance will be developed on data requirements and potential claims for ATAm, and how demonstrated treatment benefits should be factored into the benefit/risk assessment for veterinary medicines….' The CVMP has established a specific ad-hoc expert group on vaccine availability (CADVVA) responsible for implementing CVMP's actions in this area, which are therefore now not included in the direct scope of the antimicrobials strategy.
253	4	Comment: Aim 5 – responsible use. One barrier to promoting more responsible and prudent use is the narrow phrasing in the Regulation that VMPs have to be used according to the MA/SPC. In some cases, we know that the dose can be lowered or the duration	The CVMP encourages veterinarians to prescribe in accordance with the evidence-based SPC. In cases of suspected lack of efficacy due to an inadequate dosing regimen, then this should be reported through the pharmacovigilance system.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		can be shortened, but this is currently not allowed to do under the Regulation. Further to this, in order to minimise sales and spillage, veterinarians should be allowed to break up the outer package (while ensuring the inner package remains undamaged and given all extra information to the client). Some veterinary antimicrobials are only available in too big packages, which leads to a large amount of left-overs that the owner has to throw or is tempted to self-medicate their animal when having a problem in the future. Proposed change: investigate to allow veterinarians the possibility to divert from the SOP for well justified reasons, such as to allow to break up outer packages to avoid spillage and self-medication.	The CVMP prefers to address this issue by providing recommendations to marketing authorisation holders in order that they supply their products in the appropriate pack-size. If the outer packaging is broken, important information included on the product label may be lost and storage conditions breached. Guidance has been made available in the Q&A on the CVMP guideline on the SPC for antimicrobial products (EMA/CVMP/414812/2011- Rev.2) and is also included in Annex II of the draft of the revised guideline EMA/CVMP/383441/2005-Rev.1.
255	5	Comment: Include distribution in Aim 5. As the Regulation (EU) 2019/6 includes not only utilisation, but also pre-market actions Proposed change (if any): Support responsible use and distribution of antimicrobials both in accordance with marketing authorisations and under the cascade	Not accepted. Although the CVMP supports GDP, its implementation does not fall within the CVMP's remit. In addition, GDP is not specific to antimicrobial VMPs; therefore, it is preferred not to reference it in this antimicrobials strategy.
279 - 281	5	Comment: By when does the CVMP plan to develop the reflection paper for the availability and characteristics of diagnostics test? (by 2022? 2023?)	The timelines for development of the reflection paper on diagnostic testing will be set out in the CVMP's work plan, which is updated annually. The intention is to develop the

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			paper within the next period to 2025. The start date is dependent on competing priorities.
287	4	Comment 'The overall public health goal of the action plan is to ensure, for as long as possible, continuity of treatment and prevention of infectious disease with effective safe medicines that are quality-assured, used in a responsible way and accessible to all who need them.' This is a bit confusing. Antibiotics should be used for treatment. Other products like vaccines or ATA can be used for prevention. Moreover, prevention against infections, embraces animal husbandry, effective biosecurity and better feeding and housing conditions.	The text is a citation from the WHO in relation to its Global Action Plan https://www.who.int/antimicrobial-resistance/global-action-plan/en/