27 July 2016
EMA/CVMP/CHMP/390632/2016
Committee for Medicinal Products for Veterinary use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health' (EMA/CVMP/CHMP/231573/2016)

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

Stakeholder no.	Name of organisation or individual
1	Alliance to Save our Antibiotics
2	Health Care Without Harm Europe
3	Public Advice International Foundation
4	Association of Veterinary Consultants (AVC)
5	Federal Ministry of Food and Agriculture (BMEL)
6	Virbac
7	National Veterinary Technical Society (SNGTV)
8	European Group for Generic Veterinary Products (EGGVP)
9	Syndicat National des Vétérinaires Conseils (SNVeCo)
10	BVA
11	IFAH
12	Federation of Veterinarians of Europe (FVE)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The Alliance was disappointed that the European Medicine Agency's (EMA) failed to recommend a ban on the use of colistin, a last-resort human antibiotic, in livestock farming. This is despite the EMA's assessment that resistance to colistin is "likely" to be transferring from farm animals to humans in the European Union, and despite the EMA's own position, which is in favour of a ban on the blanket use of the colistin for farm animals. If the recommended target is achieved - which would result in an overall reduction in use of about two thirds - over 100 times more colistin could still be used in farm animals than in humans in the EU. I would be very interested in hearing your thoughts as to why the EMA decided against recommending a ban on colistin in farming?	For an explanation of why withdrawal of marketing authorisation is not recommended, see section 10.1 of the report.
2	Colistin is a last resort antibiotic for human health, therefore should not be used at all in animals - this measure should be taken for all last resort antibiotics for human health. Concrete prophylactic guidelines are further needed at EU level to tackle the spread of resistance from animal to humans, including awareness and education on prophylactic actions. National authorities must implement thorough inspection and data collection systems for the sales of antibiotics at national level, and report this data to the EU. To improve prescription and antibiotic use in the veterinary and human sectors, the marketing authorisation file should include an AMR risk evaluation for each antibiotic on the market. The industry should provide this to EMA when they need to renew the marketing authorisation.	The decision as to whether an antimicrobial substance should be used in animals should be based on a benefit-risk assessment that takes into account the benefits to animal health as well as the risk to public and human health. Various measures are in place in the EU to address the issues raised: The Commission has published Guidelines for prudent use of antimicrobials in veterinary medicine (2015/C 299/04) The ESVAC project monitors sales of antimicrobials in the EU For new antimicrobials coming to

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		market for use in food-producing animals, data on AMR are required in line with VICH GL 27.
3	PA International commends the European Medicines Agency (EMA) and the Antimicrobial Advice Ad Hoc Expert Group (AMEG) for their dedicated work and commitment to tackle antimicrobial resistance (AMR) and particularly the grave danger posed by resistance to colistin. In this regard, a tax on colistin and all veterinary antibiotics should be implemented as proposed by Lord Jim O'Neill and the UK Review on AMR. Colistin is critically important to human health. However, the report indicates that colistin is more widely used for animal health than for humans: its widespread use in agriculture thus requires further measures aside from more stringent access. Taxation would greatly and with immediate effect reduce the unnecessary use of colistin and all antibiotics. The increased cost would serve as a disincentive for those who would use antibiotics for prophylactic and growth promoting purposes. As indicated in the report, the importance of colistin as a last-resort drug is growing as more cases of multi-drug resistant bacterial infections are being observed in humans. Continued widespread use of colistin in animals will foster resistance that can be transmitted through the food-chain and fundamentally undermine human health. The report explicitly states that colistin could be replaced by other antibiotics under certain circumstances. Therefore, limiting access would promote human health without undermining animal health. A stricter regulatory framework and taxation should not be applied solely to the veterinary use of colistin. All critically important antibiotics for human health also used in animal rearing should be given category 2 classification if they are not banned, and the tax on veterinary antibiotics should be applied universally. The announcement of NDM-9 by 'The Lancet' in February 2016 and the recent detection of colistin resistant (MCR-1) E Coli in a woman in the United States demonstrate not only the importance of stringent rules and restrictions on colistin and other veterinary drugs but also of controlling the	Differential taxes on antimicrobials have been introduced in some MSs. In addition, taxation might require changes on the legislation at national level which would require years to be implemented in all EU countries.

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	use of antibiotics in the food chain. NDM-9 makes bacteria resistant to β-lactam antibiotics, including carbapenems. In February 2016, The Lancet announced that a bacteria had been found with both NDM-9 and MCR-1. This bacteria was practically unstoppable because it was resistant to virtually all antibiotics. In China top economic advisers – part of a unique High Level Multi-stakeholder Working Committee on AMR – have indicated a 467 bn USD initial economic damage of a potential AMR outbreak in China – followed by serious impact on global trade. In a draft (unpublished) report the authors advise the Chinese Government to introduce an immediate tax on all antibiotics used for any other purpose than to combat a disease. This should also stop the use of formally allowed use of antibiotics for growth promotion.	
5	DE is very concerned by the rising amount of antibiotic resistance and thus has launched its first antibiotic resistance strategy DART as early as 2008. This strategy has been revised in 2015. In order to reduce the emergence and spread of antibiotic resistance, DE believes all antibiotic use should be reduced to the therapeutic minimum. As this cannot be defined due to a lack of relevant data, DE established a benchmarking system to reach this goal. This proves to be effective without defining quantitative reduction targets. DE is in favour of firm restrictions on the use of certain antibiotics but against the ban of their use in veterinary medicine. DE does not agree with the definition of quantitative targets set without scientific justification. With phenomena like cross-resistance and co-selection and without explanations for the differences in Colistin-use between member states there is no justification for this new mode of action. Just like human doctors, veterinarians have the principle right of therapeutic freedom. The producers of authorised veterinary medicinal products containing Colistin have a right to put them on the market. Sound scientific data is needed to justify any restriction of the rights of both professions rather than a risk assessment based on expert opinion due to lack of this data. The latter would be overstressing the precautionary principle. DE is not convinced that the presented target is the only way to achieve a reduction in colistin	Point 9.1.4 of the updated advice provides the justification for setting targets. Although benchmarking has been demonstrated as an effective means to reduce antimicrobial use by focusing on farms that have the highest use, extensive resource is first needed to put required systems in place. High level targets, especially when supported by governments, have been shown to be a motivator to reduce antimicrobial use. Member states can additionally propose national measures according to local circumstances to assist in achieving

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	use in veterinary medicine. The document should therefore be augmented with other possible targets (e.g. number of treatments/number of animals) and management options. As stated in the Annex, all obvious management options to achieve the target proposed in the document are not feasible. To define a target roposlalacking practical means to achieve it will not result in reaching the goal, in this case preserving the effectivity of colistin.	the proposed target. The RONAFA report (to be published Dec 2016) will propose a range of measures to reduce the use of, and need to use, antimicrobials in food producing animals.
8	EGGVP supports the correct and prudent use of antibiotics and shares the general concerns related to resistance development. EGGVP therefore supports initiatives and measures based on a thorough scientific evaluation, and appreciates the extensive efforts and evaluation of the available data concerning colistin by AMEG. However, EGGVP is of the opinion that AMEG's proposed restrictions on the use of colistin in veterinary medicine are being set too rapidly and too drastically, while these may not be the preventing factor of the eventual development of resistance in humans. If such measures are implemented, colistin - a valuable, safe, well established and necessary veterinary medicine - will be disproportionally restricted. As a consequence, one can very possibly expect an increased use of: - other critically important antibiotics for human use, or - antimicrobials with a risk to potentially increase co-selection, and therefore with counterproductive results for public health, or - environmental contaminants such as Zinc Oxide, which will ultimately have a more negative influence on the situation at the human side. In EGGVP's view, a more effective approach would be by improving stewardship of polymyxins in hospitals and in agriculture. As a general comment, EGGVP believes that more emphasis/focus should have been given to the need for a One Health approach, i.e. by urgently re-considering Selective Digestive tract Decontamination with colistin in hospitals, and promote alternatives to polymyxins to be used.	We fully support the WHO global action plan regarding the need for One Health approach and international cooperation. Consideration of restrictions of use of colistin in human medicine are not within the ToR of the mandate. ECDC has considered these issues: European Centre for Disease Prevention and Control. Plasmid-mediated colistin resistance in Enterobacteriaceae. Stockholm: ECDC; 2016. (link)

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	Similarly, references to global action are also weak / absent in the advice. It is EGGVP's opinion that of major concern is the incorrect use of colistin outside Europe (low doses, long duration, poor animal husbandry, etc.). This problem should be addressed first and on a global level. Positive in this respect is the news that the use as growth promotor would be possibly banned in China, which should be considered much more important as impacting factor than the proposed European restrictions.	
10	BVA is grateful for the opportunity to respond to this consultation, which we have formulated via our Medicines working group. Colistin use is low as indicated on a national basis in the EMA document and is likely to have declined further since 2013 - the year referred to in the paper. UK use is already below the EMA target and the Pig Veterinary Society regards Colistin as a last resort (Group 3) active. BVA urges that decisions on restriction of the use of antimicrobials are made on the basis of scientific evidence.	Noted.
11	IFAH-Europe welcomes the opportunity to comment on the updated advice and appreciates the extension of the consultation period to one month. The restrictions for colistin emphasise the need for novel antibacterial agents for use in the treatment of animal diseases. There are few alternatives available for the treatment of enteric disease and of those, each has issues A substantial investment will be needed to discover and develop new, innovative products for use in treating animal diseases that are clearly differentiated from products used in human health. From literature review, the AMEG report mentions that « the mcr-1 gene has been present in some bacterial species from animals for decades » (lines 146-147). Moreover, according to a recent European retrospective study on E. coli and Salmonella spp strains isolated from cattle and pigs between 2004 and 2014, the mcr-1 gene was already present in 2004 and no trend towards an increase of this gene prevalence was noticed (El Garch et al, 2016). In front of these data, the AMEG report indicates that « the overall prevalence of colistin resistance in animals remains – so far and with some exceptions – low in food and in animals in the EU/EEA » (lines	The finding of plasmid mediated *mcr-1* is highly concerning and, as stated in the previous advice, it requires a reconsideration of the risk assessment measures.

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	144-145). Thus the recently discovered mcr-1 resistance mechanism does not seem to have induced an important increase of resistance prevalence to colistin in animal pathogenic and commensal bacteria over time in the EU/EEA. The situation outside the EU/EEA may be different, particularly in China where sub-optimal colistin dose regimens for growth promotion have been reported, along with higher rate of resistance to colistin (AMEG report lines 858-860, Richez and Burch, 2016). In human medicine, the AMEG report mentions that « colistin resistance has been emerging rapidly following its reintroduction » (line 376). Therefore the respective roles of animal use (in EU/EEA conditions) and human use of colistin on the risk of resistance emergence in humans remains debatable. The setting of a quantitative limit on use is we believe unfocussed and a poor risk management measure particularly given the current inability to monitor consumption in real time. The lag between consumption and the compilation of annual use data leaves authorities with a difficult task. Particularly as there are also limited alternative antibiotic treatment choices for some conditions. We believe that other risk management measures may have been more suitable. References El Garch F. et al, 2016. No trend towards increasing mcr-1 prevalence between 2004 and 2014 in food-producing animals in Europe. ECCMID Proceedings OLB01.	Noted, it is agreed the management measures are relatively difficult to implement due to lag between antimicrobial consumption and use data collection. However a reduction of colistin usage is necessary to reduce selection pressure to avoid further spread of these transferrable mechanism and the genetic elements carrying them, once these are present. The AMEG would agree that ideally a multifaceted approach should be taken to reducing the use of antimicrobials, including measures aimed at reducing use (e.g.

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	Richez P. and Burch D, 2016. Colistin in animals : a high risk for resistance selection in Europe ? Vet. Rec. 178 (4), 101-102.	benchmarking, education, improving diagnosis) and at preventing disease (vaccination, biosecurity, etc). However, targets have been shown to be an effective motivator in the first instance to encourage these measures to be implemented according to the local situation.
12	FVE recognises that antibiotics are vital to treating and preventing the spread of disease in animals and humans. Antimicrobial resistance presents an important global economic and a societal challenge that can't be tackled by any country or public administration alone. Therefore, the problem needs a comprehensive "One Health" approach to it. That means that a holistic, multi-sectorial and global approach is needed, involving many different sectors to tackle this complex problem. FVE follows the argumentation that colistin is classified as category 2 of the AMEG classification and agrees that the use of colistin has to be reduced as much as possible following responsible and prudent use principles. However, FVE is missing in the recommendations made the 'One Health aspect' (all restrictions are in the animal health field and none are recommended in the human field) and the global aspect (resistance is much higher in other parts of the world and regulation much less, so we have to be careful not to import resistance via the travelling of humans or animals, via imported food or other animal products or illegally bought colistin which is easily available without prescription via many Asian website). In addition, seen the human increase in use of colistin and the rapid increase of resistance in human health, restrictions in the animal health field alone will not be sufficient. In order to reverse this trend, action should be taken in both sectors. FVE also put into question the arbitrary set target and desirable level of 5 mg/PCU and 1mg/PCU. As also shown in the opinion, the risk involved is much higher in certain species (such as turkeys)	See the answer above to the general comment from stakeholder 8. See the answer above to the general comment from stakeholder 5. Added in section 9.2.: *"Encouragement should be given to updating vaccine antigen content at regular intervals to reflect circulating strains."*

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	and many factors play a role such as husbandry situation, climate, authorisation of veterinary medicines per country (e.g. of zinc oxide) and availability of alternatives and vaccines. Therefore more risk-based approach e.g. per species and per region seems more effective. Reaching these set targets - without giving veterinarians better treatment tools (e.g. vaccines or alternatives) and without developing effective, fast and affordable diagnostic tests - will be extremely difficult in certain European Countries and most likely will lead either to an increase of other antibiotics used (which could be worse from a resistance point of view) or to animal health and welfare problems. FVE believes that the best alternative is prevention. Prevention is better than cure and is the best way to reduce the use of antimicrobials. Prevention of infections can be achieved using a wide variety of methods such as improving biosecurity (e.g. all in – all out), good housing and ventilation, proper management especially around weaning, avoiding the mixing of animals, good hygiene, appropriate nutrition (or feed restriction to prevent rabbit colibacillosis), breeding of robust animals, regular veterinary visits to monitor animal health and welfare, herd health plans and vaccination. Seen the current economic crisis farmers are facing currently, funds or alternative methods have to be found so that farmers can invest in prevention. Nevertheless, as it happens even when good preventive measures and biosecurity plans are carefully applied, animals still may get sick due to E. coli. It is therefore of vital importance that if animals get sick the veterinarian is able to treat these sick animals under their care and, in that way, prevent the spread of disease to other animals or people. We also suggest a much stronger recommendation that we need both in the human as animal health fields, more effective and practical diagnostics to diagnose quickly and reliably, also Gram-negative bacteria and perform fast antibiotic sensitivity testing. As also mentioned in the 'O Neill report rapid diagnostics would reduce unnecessary prescription. Both FVE as CPME (the Standing Committee of European Doctors) and CED (the Council of European Dentists) are of the opinion that Critically Important Antibiotics should only be prescribed after a proper diagnosis and sensitivity testing and as a very last resort (see joint leaflet). Research funds should be put aside	See also section 9.6.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	to urgently develop affordable, effective and rapid tests. Also urgent attention and funding is needed to develop effective vaccines such as against E. Coli and make them available in all European Countries. For example an E. coli vaccine for post-weaning diarrhoea of piglets by E. Coli exists but the current F4 E.coli has not always so good results. A vaccine covering F4 and F18 strains could be more beneficial. Additionally strains F5 and F6 are a risk for piglets in their first two weeks and should be also considered to be included in vaccines. The use of probiotics (total flora) and the use of organic acids show effect in reducing the use of antimicrobials. However, many studies show that the effects of these alternatives should not be over-estimated and other studies show that also organic chicken meat samples can be found to be contaminated with ESBL producing E. coli, and the ESBL genes and strain types were largely the same as in conventional meat samples (Cohen S et al 2012).	

2. Specific comments on text

Chapter 1 – Executive Summary (Lines 108-199)

Line no.	Stakeholder no.	Comments	Outcome
124 – 125, 220 – 222, 381 – 387	12	Comment: Oral colistin is used for prophylaxis for Selective decontamination of the digestive tract (SDD) in humans. Several studies show that this can lead to resistance transfer and therefore advise to discourage this practice and encourage alternative preventive measures. More research on alternatives to the use of colistin for the prevention of SDD should be also encouraged. Proposed change (if any): Add recommendations with alternative to the use of colistin practices for the prophylaxis of SDD.	See section 3.1 Outside of the terms of reference (TOR) (recommendations on use of antimicrobials in humans)

Line no.	Stakeholder no.	Comments	Outcome
142 – 146	8	Comment: Positive: It is recognized that despite of the presence of mcr-1 gene for many years, prevalence of resistance has not changed in veterinary medicine.	Noted.
144 – 145	12	Comment: 'Nevertheless, the overall prevalence of colistin resistance in animals remains – with some exceptions – low in food and animals. ' Proposed change (if any): Please add figures.	Figures and tables have been added in the main document, but are not included in the executive summary.
145 – 151	12	Comment: The text should more clearly distinguish findings from European and non-European countries. Now they are all summed up behind each other which give a confused view on the situation. Proposed change (if any): split clearly when talking about Europe and non-European countries	Modification in the text as follows: *"Even though retrospective studies on collections of isolates have shown that the mcr-1 gene has been present in some bacterial species for decades, data from China (>20%) and Japan (13%) indicate that the situation is rapidly changing and that the prevalence of such strains is increasing."*
148 – 149	12	Comment: 'The mcr-1 gene is present both in isolates from clinical cases of veterinary collibacillosis and in invasive human pathogens' - Proposed change (if any): Again, please add figures. As in line 151 an average is given for reasons of clarity and comparison, the numbers should also be added for the others.	See above.
149 – 150	12	Comment: 'Human carriers can become negative within one month in the absence of selection pressure. ' Proposed change (if any): The same phenome is seen in animals, please add.	The AMEG did not have this information in animal studies, so far.
153, 957	12	Proposed change: 'It is of essential therapeutic importance …'	Not accepted. Therapeutic importance is detailed in the main document (section 3.2.) See below.
157 – 161	8	Comment: Alternatives are very limited, because of resistance rates to commonly used	See 9.1.2 in the advice.

Line no.	Stakeholder no.	Comments	Outcome
		antibiotics (sulfa/trim, tetracycline, aminopenicillins) or limited authorisations for the target animal species (e.g. turkeys). In some target animal species, a restriction of the use of colistin will lead to an increased use of the more critical fluoroquinolones, which are of higher importance in human medicine compared to colistin. Of critical importance is the use of colistin in laying hens, as the alternative, the fluoroquinolones are not permitted to be given to laying hens. Losing one alternative treatment will furthermore increase the selection pressure for resistance to other antibacterials, as no rotation is possible. This could counter the improvement already reached with the use of several antibiotic classes. The replacement of colistin (local action) by systemic antimicrobials (e.g. tetracyclines, aminopenicillins) for treatment of gastro-intestinal infections could also be a cause for selection of resistant bacteria in other body tissues (e.g. lung), where the antibiotic levels are lower.	This document is not imposing a total ban but a target of maximum use (see also section 9.1.2. and 9.1.4.)
162, 775	12	Comment: 'the larger abundance of the mcr-1 gene in veterinary isolates compared to human isolates, ' Proposed change: please justify this statement with figures.	Changed: *"The more frequent isolation of the mcr-1 gene in veterinary isolates compared to human isolates up until now (Table 9), together"* See also section 5.
162 – 165	4, 7, 9	Comment: "The larger abundance of the mcr-1 gene in veterinary isolates compared to human isolates" is a speculative statement that is not based on reliable data (see Kluytmans–van den Bergh et al, 2016 which is the only reference that compares the presence of 3 strains from animals vs. 0 strain from human sources and does not conclude that there is a larger abundance of the mcr-1 gene in veterinary isolates). Proposed change (if any): This speculative (not science-based) statement should be removed from the document given that such a document should be based on proven and established facts, not speculative or oriented opinions.	Partially agreed; although selection bias cannot be excluded, we here refer to table 9. Sentence has been adapted as outlined above to avoid the implication of a potential selection bias. Details have been included in Table 9 and reference here has been made here now (both in the executive

Line no.	Stakeholder no.	Comments	Outcome
			summary and main text). Sentence has been adapted, but must be seen as a part of a structured rationale. Changed: *"The more frequent isolation of the mcr-1 gene in veterinary isolates compared to human isolates up until now (Table 9), together"*
162 – 165	8	Comment: It is typical that a larger abundance of resistance genes are observed in the group where the antibiotic is used more often, as only selective pressure will cause resistance development. This is not to be treated as equivalent to a major source for transmission. Resistance and resistance genes can develop independently in different groups when an antibiotic is used. Proposed change (if any): The statement of transmission from animals to humans is suggestive and not facts-based. Therefore it should be eliminated from the text as this should not be part of a scientific expert report. This also accounts for similar statements throughout the entire text containing wordings such as possibly, likely etc.	Partially agreed; although selection bias cannot be excluded, we here refer to table 9. Sentence has been adapted as outlined above to avoid the implication of a potential selection bias. Details have been included in Table 9 and reference here has been made here now (both in the executive summary and main text). Sentence has been adapted, but must be seen as a part of a structured rationale. Changed: *"The more frequent isolation of the mcr-1 gene in veterinary isolates compared to human isolates up until now (Table 9), together"*
172, 393, 443, 492, 1095, 1236,	4, 7, 9	Comment: "In April 2016 the CVMP recommended the withdrawal of the marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances"	Agreed. The text has been amended.

Line no.	Stakeholder no.	Comments	Outcome
etc.		This statement appears in several places in the document and seems to be only valid for oral use, not for parenteral use Proposed change (if any): “In April 2016 the CVMP recommended the withdrawal of the marketing authorisations for all veterinary medicinal products for oral use containing colistin in combination with other antimicrobial substances”.	
174 – 178	4, 7, 9	Comment: it is stated that some MS have a low level or no use of the substance, suggesting that there is scope to decrease the overall use of colistin within the EU. If we look carefully at the most recent ESVAC report, it shows that, for example in the UK and the Netherlands, the low level of colistin use is compensated by greater use of extended-spectrum penicillins. Amino-penicillins, therefore, are used instead of colistin, which does not mean that the overall consumption of antibiotics against Gram-negative bacteria is lower, with potentially higher risks of the emergence of other forms of resistance. Zinc oxide is also used in some Member States for the control of post-weaning diarrhoea in pigs. For example in Denmark, 500 Tons zinc oxide are given to pigs each year, which corresponds to ca. 60 millions piglets treated for 7 days; in other countries, these piglets would have been treated with colistin. Proposed change (if any): This speculative statement does not take any account of the actual situation and should be withdrawn or discussed by explaining that in countries where colistin is not used, other antimicrobials are used instead.	A crude analysis of the data from all countries that report to ESVAC (2013) does not confirm that a low level of colistin use is compensated by greater use of extended-spectrum penicillins (especially in countries with high consumption of overall mg/PCU).
174 – 178, 184 – 189	8	The wide variation of use of colistin in European countries is depending on different livestock (cattle/sheep countries vs pig/poultry countries), different climates and therefore different husbandry practices and production systems (raising vs fattening). A limit to be set for all countries does not take this under consideration.	See section 9.1.4. of the advice.
182 – 183	6	Proposed change: Complete the sentence as: “Colistin should be added to a higher risk category (category 2) of the AMEG classification except for non-oral routes (injectable, intramammary, topical formulations)	Although colistin itself is in Category 2, further restrictions on injectable, intramammary and topical formulations were not considered

Line no.	Stakeholder no.	Comments	Outcome
			necessary (see section 10.5). Section 10.5 has been revised: *"Taking into account the fact that these formulations account for less than 1% of colistin sales, are mostly used for individual animal treatment and via non-enteral routes of administration, it was considered that although colistin should be in Category 2, further restrictions on the use of these colistin formulations would not have a major impact on the risk to public health. If in future it is apparent the sales of these formulations are increasing than the possibility of the restrictions of the use should be reconsidered."*

Chapter 2 – Introduction (Lines 201-235)

Line no.	Stakeholder no.	Comments	Outcome
207 – 210	4, 7, 9	Comment: reference to the Second World War is not necessary in a scientific document intended to be discussed by representative of a unified Europe. It is stated that colistin was discovered in 1949 and that it was first isolated in 1950. Proposed change (if any): Colistin (polymyxin E) is a cationic, multicomponent lipopeptide antibacterial agent that was isolated by Koyama et al from the broth of Paenibacillus (Bacillus) polymyxa var.	Agreed, the text has been amended.

Line no.	Stakeholder no.	Comments	Outcome
		colistinus in the late 1940s (Koyama et al., 1950). It was used clinically in animals in the 1950s and in humans in the 1960s. (see mention of 1950s in line 414, Koyama reference)	

Chapter 3 - The use of colistin in human and veterinary medicine

3.1. Human medicine (Lines 237-387)

Line no.	Stakeholder no.	Comments	Outcome
248	4, 7, 9	Comment: CMS may be less toxic than colistin sulfate but any such statement should be based on scientific facts showing, e.g. that higher doses are needed to achieve therapeutic concentrations (as stated in line 296) and this is illustrated by the Ph. Eur. monographs where the minimum potency of CMS is 11500 IU/mg vs. 19000 IU/mg for colistin sulfate. In summary, if CMS is less toxic, it is probably because only part of the colistin it contains is released after administration. No comparative toxicological studies with doses expressed as IU/kg bw are available to support the assumption that “colistin methanesulfonate is less toxic than colistin sulfate”. The only valid statement is that it is less potent. Proposed change (if any): and less potent than colistin sulfate (Li et al., 2006).	Section 3.1. was revised.
260 – 261	4, 7, 9	Comment: it is stated that Polymyxin B is available in parenteral formulations and can be administered intravenously, intramuscularly, or intrathecally. In line 254, it is stated that “in the EU/EEA polymyxin B is used only for topical administration in humans”. As the CVMP’s advice is focused on European use of colistin, the statement in lines 260-261 should be withdrawn. Proposed change (if any): remove the entire statement on the availability of parenteral formulations as this is not relevant for Europe.	Section has been revised.
275	12	Comment: In April 2016, CVMP recommended the withdrawal of marketing	Although the proposal is very

Line no.	Stakeholder no.	Comments	Outcome
		authorisations for all medical products containing colistin in combination with other antimicrobial substances. In the human field, combination products are still allowed. Maybe it would be worth to investigate also there relative risk in respect to colistin resistance and multi-resistance development. Proposed change: Add a recommendation for a reflection paper on this.	reasonable, is outside the scope of the scientific advice.
304 – 305	4, 7, 9	Comment: "… express the dose (in grams colistin base and as International Units)". The dose of colistin usually corresponds to a few mg (3 to 5) per kg of body weight, i.e. about 250 mg/adult, not grams. Proposed change (if any): "… express the dose (in milligrams colistin base and as International Units)".	Agreed. Change has been made: *"express the dose (in milligrams colistin base and as International Units)".*
322 - 324	12	Comment: Both in human and veterinary medicine, we have the problem that certain products are only available on certain markets. It would be greatly helpful if alternatives to the use of colistin in both sectors would become available to use in all European countries. Proposed Change: to recommend EMA and HMA to investigate ways to make more alternatives to critically important antibiotics available throughout Europe.	The recommendation is noted, as it is already reflected in other EMA/CVMP document: there is no need to repeat it on this scientific advice.
325 – 329	8	Comment: One of the concerns is the resistance due to mutations in lipopolysaccharide B of cellular walls. It is an epigenetic selection of the strains (adaptation to the environment). It is reversible because it is a sensitivity and not a resistance issue. After termination of therapy with colistin, "resistance" by selective strains is reverted and colistin regains its effectivity towards those. A nosocomial infection requires an immediate effective antibiotic treatment. Therefore, colistin is not the best option since its use at systemic (limited) dose levels in humans is responsible for the selection of resistance. For that reason Human research is working on other alternatives which can be more effective and less toxic. Examples are Ceftazidime/Avibactam, Plazomicin, Ceftolozane/tazobactam, Imipenem/relebactam, Minocycline & Fosfomycine, some of them recently approved by FDA and EMA and already in use in hospitals. In the near	Noted.

Line no.	Stakeholder no.	Comments	Outcome
		future, the role of polymyxins compared with those newer agents should be (re)defined. These newer antibiotics, are likely to reduce the demand for polymyxins and its use in human medicine.	
353, 358, 1559, 85	10	Comment: Stratified sales data is unlikely to be accurately interpretable because of the cascade use of medicines. However, it may be able to indicate trends or work for a small number of drugs that have individual species use. Proposed change (if any): N/A	Noted.
354 – 355	12	Comment: For clarity and easy comparison with Table 1 please add between brackets the ddd/1000 inhabitants for intensive care and university hospitals. This is very difficult to read from Figure 1.	Antibiotic consumption rates are expressed in Defined Daily Doses (DDDs) controlled for the population "at risk" of receiving these DDDs, i.e. inhabitants or inhabitant-days for antibiotic consumption of a country (Table 1), but patients or patient-days for antibiotic consumption in a hospital or intensive care units (Figure 1). Table 1 and Figure 1 are therefore correct. For clarity, we added "(expressed in DDD per 1000 patient-days)" as part of the title of Figure 1.
376 – 387	8	Comment: Because of the high neuro- and nephrotoxicity, the systemic use of colistin in human medicine was limited for many years - and still is up to this date. Decades of inhalation therapy in humans for cystic fibrosis, especially in paediatrics, did not result in a high incidence of non-efficacy and resistance in parallel with veterinary use. Proposed change (if any): Line 376 "Contrary to the more recent systemic use, local higher and sufficient pulmonary	The first line of the paragraph has been changed: *"Colistin resistance thus has been emerging rapidly following its reintroduction for parenteral use in human medicine"*

Line no.	Stakeholder no.	Comments	Outcome
		colistin levels seemed to significantly prevent colistin resistance in humans. The rapid emerging colistin resistance after its re-introduction in human medicine for systemic use indicates clearly that human use triggers this resistance development. Due to the toxicity of colistin, the dose which can be administered for systemic use is limited, and inadequate low levels in the target tissue will be the main trigger for development of resistance. Colistin resistance thus has been emerging…"	

Chapter 3 - The use of colistin in human and veterinary medicine

3.2. Veterinary medicine (Lines 389–492)

Line no.	Stakeholder no.	Comments	Outcome
389 – 390	4, 7, 9	Comment: It is stated that within EU MSs, colistin and polymyxin B are authorised nationally and that the main indications are infections caused by Enterobacteriaceae in pigs, poultry, cattle, sheep, goats and rabbits. Proposed change (if any): This should be revised as polymyxin B is not authorised for food animals in the EU (no MRLs have been determined), e.g.:In EU MSs, colistin and polymyxin B are authorised nationally for food and companion animals, respectively (no MRLs have been determined for polymyxin B). Colistin is used against infections caused by Enterobacteriaceae in pigs, poultry, cattle, sheep, goats and rabbits. Colistin is also used in laying hens and in cattle, sheep and goats producing milk for human consumption. We would suggest including that "colistin is also active against endotoxins produced by some E. coli strains in the GI tract, which constitutes a major clinical advantage over other antibiotics potentially used against enteric E. coli infections."	Noted, the text has been corrected accordingly.
389	8	Comment: Polymyxin B is not authorized for food-producing animals in the EU. There is	Noted, the text has been corrected

Line no.	Stakeholder no.	Comments	Outcome
		no MRL established. Proposed change: addition: “The main indication of colistin in veterinary practice is infection of the gastro-intestinal tract caused by non-invasive E. coli in pigs, poultry, cattle, sheep, goats and rabbits. “	accordingly.
393	8	Proposed change: “…replacer diets. Colistin is of high importance in the treatment of gastro-intestinal infections in animals. Besides its high efficacy against E. coli, it has also the unique advantage to bind E.coli endotoxins, neutralising their toxicity on gastro-intestinal cells causing continuation of diarrhoea despite termination of the bacterial infection. Combinations…”	Noted but the change has not been accepted.
393 – 394	4, 7, 9	Comment: It is stated that “Combinations of colistin with other antimicrobials are available for group treatments of food-producing animals in some EU countries”. Proposed change (if any): This statement should be revised in the light of the new recommendation to withdraw colistin fixed antibiotic combinations (April 2016) for oral use. Proposed change: “Combinations of colistin with other antimicrobials available for group treatments of food-producing animals in some EU countries will be banned in the near future and only injectable forms (including intramammary forms) for individual treatments will remain on the market”.	Not accepted. Please see the comment above in regards to section 10.5.
393 – 394	8	Comment: Since April 2016, there is already a recommendation to withdraw such combinations for oral use in food producing animals, the sentence should be formulated differently taking into account this new provisions.	Accepted.
399 – 400	4, 7, 9	Comment: “As in human medicine, colistin and polymyxin B have been registered for topical administration to individual veterinary patients”. This is only true for non food-producing animals in the case of polymyxin B (no MRLs). Proposed change (if any): “As in human medicine, colistin and polymyxin B have been registered for topical administration to individual veterinary patients, except for food-	Accepted, the text has been amended.

Line no.	Stakeholder no.	Comments	Outcome
		producing animals in the case of polymyxin B, in the absence of MRLs".	
405	12	Comment: Suggest to make clear distinction between use in Europe, in North-America and in Asia (eg line 452 deals with colistin found in fishery products in China, this is not clear as the lines above and below are about Europe). Having consulted our fish veterinarians they tell us they have no knowledge of use of colistin in aquaculture in Europe. Proposed change: distinguish clearly via headers in which region of the world the use is and please also add for Asia the estimated volumes used and the Regulation applying.	Not accepted.
416 – 434, 787 – 808, 812 – 823	12	Comment: Data from Belgium (and in second piece of Netherlands) is over-represented and some is only based on studies from a very limited number of farms. Please add data on the use in the countries which have the highest use per PCU as this will help for taking a risk-based approach.	The data are presented as an example from those countries, due to the limited time available for the update of the scientific advice is not possible to provide further details from other countries.
422 – 423	4, 7, 9	Comment: It is stated that Belgian use of colistin was for indications others than those for which it is authorised, e.g. respiratory disease, peritonitis and streptococcal infections. In other parts of the document it is stated that colistin is selectively active against Gram-negative bacteria, i.e. in principle it is inactive against streptococci (which are Gram-positive bacteria). Proposed change (if any): This statement should be reconsidered in the light of actual conditions of use. We assume that respiratory diseases and peritonitis are treated by parenteral administration, i.e. outside the scope of the advice. Some authors may publish results on streptococcal infections but we should make sure that this kind of publication has been peer-reviewed and confirmed by other results. It is suggested to simply withdraw the statement about streptococcal infection and add that other indications are treated by injection, not colistin given orally.	Parental administration is not outside the scope of this scientific advice. See changes in the text.
439 – 440	4, 7, 9	Comment: "43.2% were oral solution (powder for use in drinking water), 42.4% were	The reference to the pharmaceutical

Line no.	Stakeholder no.	Comments	Outcome
		premix (premixes for medicated feeding stuff) and 14.0% were oral powder (powder to be administered with the feed)." We assume that oral solutions are liquid forms to be mixed with drinking water and that oral powders are powders intended to be mixed with drinking water, reconstituted milk, or feed. Proposed change (if any): 43.2% were oral solution (liquids for use in drinking water), 42.4% were premix (premixes for medicated feeding stuff) and 14.0% were oral powder (powder to be mixed with drinking water, with reconstituted milk or feed).	forms has been corrected.
439 – 440	8	Comment: The statement "43.2% were oral solution (powder for use in drinking water), 42.4% were premix (premixes for medicated feeding stuff) and 14.0% were oral powder (powder to be administered with the feed)." may be misunderstood. Proposed change: 43.2 % were oral preparations (powders and solutions) to be mixed with the drinking water …	See above.
446 – 451	8	Comment: This shows the direct relation between a decrease in use of colistin and the increase in use of zinc oxide. Some low colistin users, such as Denmark, have high zinc oxide – an environmental contaminant - consumption rates. Replacement of colistin by ZnO is clearly demonstrated in Belgium (BelVetSac figures) Furthermore, in countries where colistin is not or poorly used (e.g. UK, NL), there is a proportionate increase in aminopenicillins use as demonstrated by the ESVAC data; this in addition to zinc oxide (which only concerns pigs). All this is very discussable and needs further thorough debate.	This matter is currently under review by CVMP.
448 – 450	12	Comment: 'This reduction seen for the second year in a row has been attributed due to start of the use of zinc oxide as an alternative for colistin use in the treatment of post-weaning diarrhoea in piglets (BelVetSac, 2015).' In some countries, for environmental reasons and reasons of cross-resistance,	Noted.

Line no.	Stakeholder no.	Comments	Outcome
		a substitution with zinc oxide is not acceptable. See also FVE position paper on this issue: http://www.fve.org/uploads/publications/docs/016_fve_opinion_on_zinkoxide_adopted.pdf	
452 – 455		Comment: Please add data on use in aquaculture in Europe.	No data available.
459		Proposed Change: We suggest adding the EU average to the graph.	It is not representative in the picture.

Chapter 3 - The use of colistin in human and veterinary medicine

3.3. Antibacterial effect (Lines 494-541)

Line no.	Stakeholder no.	Comments	Outcome
537 – 541	4, 7, 9	Comment: It is stated that it is unlikely that the diversity of gut microbiota and their intrinsic difference in antibiotic susceptibilities will ever allow a PK/PD approach to be sustainable in limiting the spread of (multi)resistance in non-target bacteria. Some subpopulations among wild type strains (e.g. 3 % of 539 wild type *P. aeruginosa* strains) have a slightly increased MIC (4 µg/ml) and thereby jeopardising safe PK/PD targeting if such bacteria are clinically involved (Skov Robert, personal communication). In the references used by CVMP (Guyonnet et al, 2010; Richez & Burch, 2016), it is clearly demonstrated that colistin concentrations reach far higher levels that the common MICs found for susceptible bacteria (e.g. about 30-60 µg/ml when MICs are usually in the range 0.125 -1.0 µg/ml for *E. coli*). This should prevent the emergence of resistant strains. In addition, the CVMP assessment on colistin residues (EMEA/MRL/815/02-Final) reports that in healthy human volunteers receiving daily oral doses of 0.45 g colistin sulfate for 3 consecutive days, volunteers were progressively recolonised by colistin-susceptible enterobacteriaceae in the days following the	Agreed, the text has been deleted. These considerations were in relation to use in humans.

Line no.	Stakeholder no.	Comments	Outcome
		withdrawal of treatment. With the exception of one individual carrying Proteus, none of the volunteers was recolonised with colistin-resistant bacteria in the course of the study. The sizes of the group D streptococcal population, the staphylococcal population, yeasts and total anaerobes were not significantly affected by the treatment. So therefore data are available that should be used rather than purely speculative assumptions not proven scientifically. Proposed change (if any): This statement is purely speculative and should not appear in a scientific assessment.	

Chapter 4 - Resistance mechanisms and susceptibility testing

4.1. Resistance mechanisms (Lines 543-637)

Line no.	Stakeholder no.	Comments	Outcome
578 – 587	12	Comment: Instability studies – please add the studies that show similar effect on the animal health side.	Comment is not clear.
637, 821 – 823, 869 – 871	4, 7, 9	Comment: Reference is made to the occurrence of the mcr-1 gene in bacteria isolated from turkeys. This statement should probably be completed by some tentative explanations, e.g. by describing that colistin is used in turkeys by nebulisation to control some forms of sinusitis. This extra-label use, not validated by PK/PD assessments, may create conditions conducive to the emergence of resistance due to the low concentrations likely to be reached, except at the site of infection. Proposed change (if any): Reference to apparently increased resistance in turkeys should be completed by comments on possible extra-label uses of colistin in this species.	Accepted. Text added: *"The suggested use of colistin in turkeys by nebulisation is of concern, but the AMEG could not find relevant papers on this practices. It is not possible to speculate on this off-label use and the onset of resistance."*

Chapter 4 - Resistance mechanisms and susceptibility testing

4.2. Susceptibility testing (Lines 638-758)

Line no.	Stakeholder no.	Comments	Outcome
650 – 655	4, 7, 9	Comment: It is stated that EUCAST clinical breakpoints for Enterobacteriaceae are ≤2 µg/ml. In other parts of the document the 2 µg/ml value is presented as an epidemiological cutoff value (ECOFF), which is correct. As described in Richez & Burch (2016), colistin concentrations far higher than 2 µg/ml are reached at the site of action (GI tract) with the doses approved in Europe. The 2 µg/ml value is therefore an ECOFF useful to evaluate the emergence of mutant bacterial populations, but certainly not a clinical breakpoint for oral use. Clinical breakpoints for oral use remain to be defined by the scientific community for colistin in the different target species against wild type E. coli populations. This value is most probably at least 10 µg/ml, but in no case should 2 µg/ml be considered as a clinical breakpoint. Proposed change (if any): "EUCAST epidemiological cut-off values (ECOFF) for Enterobacteriaceae (E. coli and Klebsiella spp., but excluding 650 Proteus spp., Morganella morganii, Providencia spp., and Serratia spp.), P. aeruginosa, and A. 651 baumannii are ≤2 µg/ml.	It is an ECOFF and no clinical breakpoint is defined by EUCAST.
350 – 652	8	Comment: Local colistin concentrations much higher than 2µg/ml are obtained in the gastro-intestinal tract as colistin is not absorbed and the entire dose passes through the intestines.	Noted.
729 – 733, 754 – 758	4, 7, 9	Comment: Table 4 and Table 7 accurately consider clinical breakpoints for CIP and CTX but use 2 µg/ml as clinical breakpoint for colistin (see the comment above on ECOFF vs. clinical breakpoint). These tables therefore overestimate the percentage of resistant strains and give an erroneous figure of the actual situation (strains with an MIC of e.g. 8 µg/ml, i.e. considered as resistant from an epidemiological point of view, would be killed in the gastro-intestinal (GI) content with conventional colistin doses since local concentrations may reach about 30 - 60 µg/ml and colistin is a concentration-	Disagreed.

Line no.	Stakeholder no.	Comments	Outcome
		dependent bactericidal substance). Proposed change (if any): These tables should be withdrawn until colistin clinical breakpoints have been determined. Only comparisons based on ECOFF are scientifically justified.	

Chapter 5 - Possible links between the use of polymyxins and other antimicrobials in animals and resistance in bacteria of animal origin (Lines 759–871)

Line no.	Stakeholder no.	Comments	Outcome
762 – 765	8	Comment: Support: Despite the abundant use in veterinary medicine for over 50 years, a retrospective analysis of bacterial collections showed that transmission of colistin resistance in Gram-negative bacteria via horizontal gene transfer or sustained clonal expansion has not been substantial in the EU/EEA.	Agreed, however we do not know as much about the recent introduction of transferrable mechanisms and the changes this might lead to in terms of selection.
803 – 806	4, 7, 9	Comment: It is stated that resistance increased in Belgium in 2010 but in the next sentence colistin resistance is considered very low over the period 2011-2014 Proposed change (if any): These inconsistent statements should be either considered as not scientifically relevant, and then withdrawn from the document, or submitted to a critical analysis.	Corrected: *"In commensal E. coli from Belgian pigs and with the exception of a very slight increase in 2013, colistin resistance is considered very low over the period 2011-2014 (CODA-CERVA, 2015)."*
809 – 810	8	Comment: EGGVP would emphasize on the fact that even in the presence of mcr-1 there are still no signs of clinical resistance in the field. Resistance levels in veterinary medicine are very debatable and probably overestimated (due to the absence of clinical breakpoints), although already being and remaining at a very low level. The PK/PD rules that show that bacteria with a MIC at 8 µg/ml are killed with the doses used in EU are supported by facts. Using the current authorised oral doses, clinical efficacy has been demonstrated while MICs raised up to 8 µg/ml (Richez and Burch 2016). Cases of	Noted.

Line no.	Stakeholder no.	Comments	Outcome
		non-efficacy have rarely been reported. Without the correct breakpoints and tools, it will make no sense to make prior sensitivity testing mandatory (which is furthermore not workable due to the urgent nature of the infections to be treated).	
844	12	Comment: 'In China, in Taiwan and in France,…' Proposed Change: Please structure according to region, now it is very difficult to follow.	Not accepted.
856 – 859	12	Comment: Details on use of colistin Proposed change: Add to chapter 3.2 on Use of Colistin in Veterinary Medicine	Not accepted.
871	12	Comment: Some studies also looked at colistin resistance in wild animals (which never were treated with colistin). It might also be useful to add the results of these studies. In addition, when existing, would also be useful to have data on resistance from organic farms, which never treated with antibiotics.	Noted.

Chapter 6 - Impact of use of colistin in food-producing animals for animal and human health (Lines 872-940)

Line no.	Stakeholder no.	Comments	Outcome
872 – 940	8	Comment: Decades of veterinary use, during which practically no cases of non-efficacy have been observed, show that this substance has been used in a responsible way by the veterinary sector. The overall prevalence of colistin resistance in animals remains, so far and with few exceptions, very low in food and in animals in the EU/EEA. Despite the presence of mcr-1 resistance gene for more than a decade years in Europe, no proven link can be established between the use of colistin in animals, the presence of the mcr-1 gene and the transfer to humans in Europe. It is a very acceptable assumption that the mcr-1 gene exists already during decades, only after its detection multiple investigations have been done. There is no increase in resistance in veterinary medicine linked to the mcr-1 gene in Europe, only the reporting rate of single detected isolates of conserved bacterial strains has increased. Its role in the development of colistin resistance in veterinary medicine is therefore very doubtful, especially when	

Line no.	Stakeholder no.	Comments	Outcome
		used as currently required in Europe.	
903 – 904	8	Comment: Aminopenicillins are no alternative, due to high resistance profiles in pig and poultry in particular countries.	Accepted. The text has been changed accordingly. This comment seems to contradict the comment on the possible substitution of colistin by aminopenicillins.
924	12	Comment: 'The mcr-1 gene has been found … ' Proposed Change: please add figures	This information is already in the table.
932 – 934	4, 7, 9	Comment: It is stated that, according to Kluytmans–van den Bergh et al., 2016, mcr-1 is substantially more sparse in humans compared to animal isolates, rendering plausible the hypothesis that it might have originated in animals then spread to humans. After reviewing the publication by Kluytmans–van den Bergh et al., 2016, it appears that mcr-1 was found in only 3 strains from animals, 2 of which in samples from animals of the same group. The authors do not in any way conclude that the presence of 2 or 3 strains from animals vs. 0 from humans shows that mcr-1 was substantially more sparse in humans compared to animal isolates, and do not put forward the hypothesis that it might have originated in animals then spread to humans. Proposed change (if any): Speculative or erroneous statements should not appear in the document and should not appear in the final version.	Not accepted.
936 – 937	8	Comment: indicated by the fact, that all travellers that were tested positive for mcr-1 upon return were negative after one month. Two facts of importance are reported: the patients were infected during travelling oversea and mcr-1 resistance gene is instable when the selective pressure is withdrawn.	Noted.

Chapter 7 - Conclusions on updated literature review (Lines 941-971)

Line no.	Stakeholder no.	Comments	Outcome
946 – 948	4, 7, 9	Comment: It is stated that the number of reports is increasing very rapidly with a recent increase in animal sources, although the relative proportion amid human clinical isolates in the EU/EEA remains fairly low (less than 1%), so far. It is difficult, only a few months after the first report of the presence of the mcr-1 gene, to conclude that the proportion of resistant bacteria from animal sources is increasing faster than for humans. Extensive investigations have been conducted in 2016 in veterinary medicine and it is true that the number of reports is increasing very rapidly on the animal side, but this does not mean that the proportion of resistant strains is lower for human strains, but simply that fewer publications have been produced. To add “so far” at the end the sentence may be considered as speculative and should be withdrawn. Proposed change (if any): Following discovery of the horizontally transferable colistin gene mcr-1 in 2015, the number of reports is increasing very rapidly, especially from animal sources, as a number of Member States are starting to look for the presence of this gene.	Not accepted.
949 – 950	4, 7, 9	Comment: It is stated that there is an indication of limited spread of colistin resistance from food-producing animals to human patients, and to a lesser extent vice versa. Proposed change (if any): The results described in China indicated limited spread of colistin resistance from food-producing animals to human patients, and to a lesser extent vice versa. This is not supported by similar data in Europe.	Not accepted.
962 – 963	4, 7, 9	Comment: “some MSs having a low level, or no use of the substance, suggesting that there is scope to decrease the overall use of colistin within the EU” See our comments above about 174-178. Proposed change (if any): This statement should be revised with a critical evaluation	Not accepted. Please see the comment above.

Line no.	Stakeholder no.	Comments	Outcome
		based on a risk assessment since the possibility of decreasing use of colistin described here is based on substitution of colistin by aminopenicillins or zinc oxide, which may not be considered as an improvement regarding reductions in resistance to antibiotics in general.	

Chapter 8 - Profiling of the risk to public health resulting from the use of colistin in animals in the EU (Lines 972-1037)

Line no.	Stakeholder no.	Comments	Outcome
1023 – 1030	4, 7, 9	Comment: This part is not a risk assessment, but rather a hazard determination. Proposed change (if any): this section should be placed in chapter 8.1 (Hazard identification)	Not accepted. The text in this section is an integration of sections 8.1, 8.2 & 8.3.

Chapter 9 - Risk Management options (Lines 1038-1282)

Line no.	Stakeholder no.	Comments	Outcome
1038 – 1282	8	Comment: It is EGGVP's opinion that, under a One-Health approach, this should have been considered also: As mentioned in the updated AMEG report, use in human medicine, such as for Selective Digestive tract Decontamination (SDD) can result in the rapid spread of colistin resistance in hospitals (line 383). The recent USA-case (McGann et al 2016) probably can be considered an example of this, as in the United States it is very unlikely that there is any link with the veterinary use of colistin. Moreover, this is confirmed by the often clonal nature, the nosocomial character of colistin resistance in humans and the prior consumption of colistin as in cases of	Noted, however outside the scope of this scientific advice.

Line no.	Stakeholder no.	Comments	Outcome
		Acinetobacter baumanii (line 370). If SDD is undertaken in hospitals, alternatives to polymyxins should be used. Proposed change: New chapter under section 9: “Recommended risk management options for colistin in human medicine: - The use of colistin in human medicine for Selective Digestive tract Decontamination should be reconsidered urgently (not to wait to see the results of current measures in 3 or 4 years).”	
1039	8	Comment: This advice deals with the use of colistin in human and veterinary medicine. The target of risk management options should be clarified in the title. Proposed change: Recommended risk management options for colistin in veterinary medicine	Accepted.
1040 – 1050	8	EGGVP would like to further emphasize on the responsible use of antibiotics in general, prior to setting very restrictive limits based on “sales breakpoints” in all MS. This may not only have severe consequences for animal health, welfare and human health, but could also be questioned as Member States with high swine and poultry population will be discriminated against versus those countries where sheep and cattle play a bigger role. Consequently the use of the same maximum 5 mg/PCU for every country is artificial and difficult to justify. Correct use as described in the current revised European SPC’s should be the rationale, and close monitoring of colistin use and regular resistance evaluation (stewardship) seems to be the correct risk management option. We would like to highlight the approach taken recently in Japan as an example of continuous monitoring/surveillance in combination with good “stewardship”, which EGGVP fully supports. In this country, after the Chinese MCR-1 report, authorities checked 90 E.coli strains for colistin-resistance, from 9308 E.coli strains previously collected by JVARM (Japanese Veterinary Resistance Monitoring System in the Field of	The aim of the RMO is to reduce use of colistin. It is inevitable that since the substance is predominantly used in pigs and poultry, the impacts will be greater in countries with higher populations of those species. Good stewardship, surveillance and monitoring of colistin resistance are recommended by the AMEG; however, following the risk profiling it was considered that a more pro-active approach including targets is also necessary. Member States with lower

Line no.	Stakeholder no.	Comments	Outcome
		Animal Hygiene) between 2000 – 2014. MCR-1 was detected on 2 strains from 2008 and 2010 respectively. With these results, and as there was no increasing tendency of colistin resistance ratio since 2008, the Japanese authorities have considered that colistin is used appropriately under current Japanese legislation. Monitoring and surveillance are permanently ongoing in order to evaluate if the current measures continue to be adequate.	populations of pigs and poultry may consider the possibility of achieving less than equal to ≤1 mg/PCU.
1042	6	Proposed change: Complete the sentence as: "Colistin should be added to a more critical category (category 2) of the AMEG classification except for non-oral routes (injectable, intramammary, topical formulations)	Not accepted. Please see the comment above in regards to section 10.5.
1047 – 1048, 1166 – 1169	4, 7, 9	Comment: Use of colistin should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to antimicrobials in category 1. Antibiotics of category 1 include macrolides (inactive against E. coli), natural penicillins (inactive against E. coli, inactive orally), narrow-spectrum β lactamase penicillins (unavailable for oral use), rifamycin (not available for oral use), tetracyclines (high degree of resistance in E. coli). Therefore, use of substances in this category is not an option. The classification of colistin in category 2 should therefore be reconsidered as there is no possibility (or only very limited possibility) of using antibiotics of category 1 in the treatment of enteric infections caused by susceptible non-invasive E. coli. In addition, the classification of colistin in category 2 would be considered by veterinarians as placing colistin at the same level as fluoroquinolones (active against E. coli) and C3G / C4G (also active against E. coli). This would be counter-productive as it might simply result in a transfer from colistin to FQ and C3G / C4G. Proposed change (if any): To revise the proposal to classify colistin in category 2 as this substance will de facto remain a first-line antibiotic in almost all cases and classification in Category 2 would be counter-productive.	Partly accepted the text re-phrased: *"Use of colistin, fluoroquinolones and 3rd- and 4th-generation cephalosporins should be reserved for use when there are no effective alternative antimicrobials for the respective target species and indication."* The AMEG's overall categorisation might need to be updated according to the latest considerations on some classes of antimicrobials (e.g. colistin/polymixins, aminoglycosides, aminopenicillins)
1077	12	Comment: also rabbits and laying hens. Laying hens have a problem that you cannot	Poultry includes laying hens. The

Line no.	Stakeholder no.	Comments	Outcome
		treat them with many antibiotics due to the withdrawal time. Colistin is one of the only (and in some countries, the only option) for treatment. Proposed Change: add rabbits and laying hens	main uses only are listed here.
1083 – 1085	2	Even if you decrease doses for other antimicrobials as well, resistance occurs at lower doses - therefore doses must be increased again to have a therapeutic response to solve the problem.	The intention is to reduce the number of courses administered, not the dose rate.
1083 – 1085	12	Comment: we suggest adding at the end of the sentence ' of all classes, taken into account the balance between protecting public health and the potential impact on animal health'	This is addressed in the first bullet.
1086 – 1087	12	Comment: FVE completely agrees that we should eliminate prophylactic use but we can only do this if we increase our diagnostic methods. Therefore, a specific sentence should be added. Proposed Change: Add bullet point on need both in the human as animal health fields, more effective and practical diagnostics to diagnose quickly and reliably, both Gram-negative and Gram-positive bacteria and perform fast antibiotic sensitivity testing.	Agreed that diagnostic methods are important but these are not the only management options here. The need for diagnosis is better addressed in section 9.2.
1098	12	Comment: We suggest to change the sentence slightly to ' As colistin is used in all the major food-producing species and increasingly more in humans, measures in only one sector or species would not provide the expected results in term of reduction of use and resistance. '	Not accepted. This section relates to the considerations in regards the RMO for veterinary use.
1103	12	Comments: We believe risk based targets should be set, not just an arbitrary reduction measure without taking into account the most risky factors/species. As said in line 1130 there is insufficient information to establish the feasibility of such a measure in all countries and the impact of those intended reductions on colistin resistance.	Disagreed. Each MS can use colistin as required, so long as recommended levels are not exceeded. It would be possible for those member states where the surveillance systems and data are available to also establish more risk-based targets by species/ production class. (See general

Line no.	Stakeholder no.	Comments	Outcome
			comments).
1105	12	Comment: add extra bullet point. As shown by the report, both in human and veterinary medicine, we have the problem that certain products are only available on certain markets. It would be greatly helpful if alternatives to the use of colistin in both sectors would become available to use in all European countries. Proposed Change: add extra bullet point to recommend EMA and HMA to investigate ways to make more alternatives to critically important antibiotics available throughout Europe.	Not agreed. Out of scope.
1110 – 1112	2	"The use of colistin should be reduced (…) without a consequential increase in the consumption of (other antibiotics)"- This proposal is not feasible because of the following: Resistance cannot be tackled by lowering the doses of the antibiotic (resistance can occur at lower doses, and to continue having a therapeutic effect one either increases the doses or changes the antibiotic) There is no control on antibiotic concentration, because the medicine is mixed with food/water and animals can eat/drink more or less than the target dose. We therefore propose a complete phase out of colistin from veterinary use, once colistin is a last resort antibiotic for human use.	The intention is to reduce the number of courses administered, not the dose rate. The concentration is adjusted according to the known intake of food and water.
1127 – 1129	12	Comment: In some countries with high pig and poultry production, e.g. Denmark (0.5 mg/PCU), the level of consumption of colistin is below 1 mg/PCU. Those countries massively rely on the use of zinc oxide. The use of zinc oxide is prohibited in other European countries for amongst others environmental reasons. As such this targets will be very difficult for these countries not relying on zinc oxide.	NL and UK also have low use of colistin whilst not relying heavily on the use of ZnO.
1129 – 1132	2	There are huge discrepancies among Member States (MS) due to veterinary prescription issues. "Stricter" is a vague term, taking into consideration that in some MS one can take antibiotics without prescription1, due to the lack of inspections in the pharmacies and the other suppliers.	Out of scope.

Line no.	Stakeholder no.	Comments	Outcome
		In the EU, antibiotics should be released by medical prescription only (Council Recommendation 2002/77/EC2). We therefore recommend, in order to tackle the release of antibiotic drugs without medical prescription, each MS to have its own inspection and sanction system in place at national level. This measure would also help to record data on the number of antibiotics being prescribed for both human and veterinary use.	
1133	2	3-4 year period to achieve this target is unachievable if data is not available in all MS – we propose that data requirements are standardised for all MS.	It is proposed in section 9.1.3. that data are collected in those MSs where not currently available and provided to ESVAC.
1140 – 1141	2	"Should", must be replaced by clear legislation and guidelines regarding how to implement the described prophylactic measures. This needs a proper, achievable, strategic plan.	Same as above.
1145 – 1146	2	Who is responsible for people and animals affected by the occurrence of resistance e.g. deaths? Antimicrobial resistance (AMR) is an emergent issue at global level that needs precise measures to be tackled, not trial measures. As previously mentioned, phasing out colistin from veterinary use will eliminate the risk of transferring resistant strains from animals to humans.	Phasing out does not eliminate the risk, colistin resistance can still be selected with other antimicrobials due to co-selection.
1147	12	Comment: Fully support and we would even go further – we would suggest to implement a robust surveillance system to monitor resistance both in humans, animals (domestic, wild (Dotto 2014) and imported!), and the environment all over the world together with the support of OIE and WHO.	Noted, but not in scope of this document.
1150 - 1152	2	How is this measure expected to be implemented? There is a lack of data available in some MS, and as previously mentioned, antibiotics can still be bought over the counter in some MS. It's not about "encouraging", but "demanding" and supporting the MS to provide this data - at national level, MS should have the means to provide the necessary data and have inspection and sanction protocols in place.	The resources required need to be taken into consideration.

Line no.	Stakeholder no.	Comments	Outcome
1158 – 1164	8	Comment: In some cases, the absence of treatment could be the result, which is not compliant with the important issue of animal well-being and which is clearly in conflict with the important One Health approach. The veterinarian is the animal's advocate and is obliged to help a suffering animal. Diarrhoea caused by E. coli can cause high mortality in pigs, chickens and turkeys when left untreated. Immediate and effective treatment is required in such conditions. E. coli is often resistant to several antibiotics and colistin is an antibiotic of special importance also in veterinary medicine. If colistin is effective and other antimicrobials are ineffective or of special importance (as e.g. fluoroquinolones), it is the decision of the veterinarian to choose a suitable antimicrobial to prevent suffering of the animals.	Colistin will still be available for those cases for which it is the best option. The intention is to find a balance between the need to protect public health and impacts on animal health.
1166	6	Proposed change: Complete the sentence as: "Colistin should be category 2 of the AMEG classification except for non-oral routes (injectable, intramammary, topical formulations)	Not accepted. Please see the comment above in regards to section 10.5.
1106 – 1141	8	EGGVP regards AMEG's opinion as setting too rapid and drastic recommendations. EGGVP assumes this is done under precautionary principles and, as new evidence becomes available, it may possibly allow revising these risk management measures. In particular: o Monitoring resistance development in animals and humans o Monitoring the prevalence and progression of the mcr-1 gene o Monitoring the consumption patterns of other antimicrobials in veterinary medicine But also (also crucial and not included AMEG's recommendations): o Evaluation of the referral measures included already in the Colistin products SPC's o Full epidemiological studies on the mcr-1 gene are also of outmost importance to evaluate its impact and ability to spread. Therefore EGGVP recommends:	Noted. Following the AMEG's risk profiling, we consider that more pro-active measures are needed. Targets have been demonstrated to be effective in those MSs where they have been applied, whereas the impact of SPC warnings/restrictions alone is less clear.

Line no.	Stakeholder no.	Comments	Outcome
		1. Two-step approach: EGGVP proposes a half-step that includes the study of the new data and results available two years after adoption of AMEG's advice, considering that the very rapid and strict restrictions on veterinary use may endanger animal and human health by, i.e.: • Increasing consumption of other critically important antibiotics and environmental contaminants • Increasing resistance rates in animals or humans 2. Temporarily retain classification 1: Because of the risks above mentioned, EGGVP suggests not changing the classification of colistin until the results of latest EU Referral are available and to further focus on good Stewardship and not on fixed limits 3. Reversibility of measures: if there is no obvious transmission of the mcr-1 gene from animal to human health in Europe, the recommendations for veterinary use should be reconsidered.	
1166 – 1169, 1182 – 1183	10	Comment: There is some conflation in the document of Colistin (Polymyxin E) with all polymyxins (including Polymyxin B) which is present for topical use in Surolan. The paper also makes reference to the registration of Colistin for topical use in companion animals but there is no reference to an EU licensed product. The relevant recommendations (if they were to be applied to all polymyxins) would be: a) Colistin should be added to category 2 of the AMEG's classification; the risk to public health from veterinary use is considered only acceptable provided that specific restrictions are placed on its use. Colistin should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to antimicrobials in category 1. b) Reduction in use of colistin should be achieved without an increase in the use (in mg/PCU) of fluoroquinolones, 3rd- and 4th-generation cephalosporins or overall consumption of antimicrobials. The former would not pose a problem in companion animals as the most common	The recommendations do not apply to topically applied products (see 10.5).

Line no.	Stakeholder no.	Comments	Outcome
		indication would be Pseudomonas otitis (which should have culture and sensitivity testing before treatment because empirical selection of antibiotics is not indicated). However, reduced use of Polymyxins is likely to involve increased use of Fluoroquinolones in such circumstances – although the volumes involved are likely to be very small, which could be an unintended consequence. Proposed change (if any): N/A	
1168 – 1169	2	Guidelines are needed to define the meaning of “responded poorly” or “are expected to respond poorly”.	Comment accepted. This will be addressed in future work.
1180 – 1181	2	Lowering doses will not solve the problem, and moreover will not have the expected therapeutic effect at any dose.	Noted.
1195 – 1197	4, 7, 9	Comment: AVC supports the recommendation to improve the antibiotic regimen by applying PK/PD analyses to assist in dose regimen selection, along with identifying a minimum number of days of exposure. However, until clinical breakpoints are defined and PK at the GI level are available for all species, it should be noted that considerable efforts remain to be made by the scientific community in this domain. We suggest that CVMP uses this document to promote the development of PK/PD research amongst European competent bodies (universities, national institutes, scientific organisations such as ECVPT, EAVPT, industry consortium, etc.).	Noted.
1209 – 1210	12	Comments: Vaccines are not always effective and not all vaccines are available in all EU countries.	Noted.
1262	12	Comment: ‘Treatment of individual animals is preferred.’ In certain species this will be contra-productive as explained in line 1294-1305. Proposed change: Delete.	Noted.

Chapter 11 – Figures (Lines 1317-1374)

Line no.	Stakeholder no.	Comments	Outcome
1313 – 1314	6	The AMEG report mentions that restrictions on non-oral colistin formulations (injectable, intramammary and topical formulations) « would have minimal impact on the risk to public health » (line 1315). This assessment is supported by the low relative weight of colistin sales by these routes of administration (less than 1% as represented in figure 7) and by the individual curative context of colistin use by these non-enteral routes of administration (lines 1313-1314). It can be added that following parenteral administration, colistin is excreted by glomerular filtration in the urine (Pilloud 1983, Prescott 2000, EMEA 2002). Therefore no impact on digestive flora is expected from colistin treatment either by injectable route or by intramammary route (for which the resorbed fraction, if any, would come into the bloodstream before being eliminated by renal route). Colistin is used by injectable route to treat septicaemia in cattle and pigs due to invasive E. coli. If colistin would be classified as critical by this route of administration, no alternative would remain to treat such infections apart from antimicrobials already classified as critical (fluoroquinolones and C3-C4 cephalosporins) or antimicrobials whose re-evaluation is pending and susceptible to be classified in category 2, namely aminoglycosides or aminopenicillins (including combination of amoxicillin and clavulanic acid). For example, antimicrobial resistance surveys from France and Germany show that among currently non Critically Important Antimicrobials (CIAs), only the combination of amoxicillin and clavulanic acid or gentamicin show susceptibility levels on cattle and pig enteritis E. coli regularly above 50% (Table). It must be noticed that extended-spectrum penicillins with activity against Enterobacteriaceae (including the combination of amoxicillin and clavulanic acid) might have the ability to facilitate the spread of bacterial isolates resistant to extended-spectrum beta-lactams (EMA 2015). Thus taking into account the severity of septicaemia cases requiring a parenteral antimicrobial treatment without delay, so before bacteriological analysis and	See comments above from section 10.5.

Line no.	Stakeholder no.	Comments	Outcome
		susceptibility testing, placing colistin in the category 2 of the AMEG classification whatever the route of administration would drastically reduce the options for non CIAs parenteral therapy of these diseases in cattle and pig. In previous AMEG advice on ranking of antibiotics, the route of administration was pointed out among factors to consider for appropriate risk management measures (EMA 2014). Therefore, taking into account that restrictions on non-oral colistin formulations both would have a minimal impact on the risk to public health but could have a significant impact on the risk to animal health (or induce an increase of CIAs use), we propose to exclude the non-oral formulations (injectable, intramammary, topical) from the classification of colistin in category 2. Table : Susceptibility levels of enteritis E. coli isolated from clinical cases in France and Germany Cattle Pig France1 Germany2 France1 Germany3 Ampicillin/Amoxicillin4 14% 21% 39% 29% Amoxicillin + Clavulanic acid 38% 57% 87% 86% Streptomycin 14% NA NA NA Gentamicin 79% 60% 85% 86% Tetracycline 21% 25% 28% 21% Sulfonamides 20% NA NA NA Sulfonamides + Trimethoprim 62% 50% 45% 44% Spectinomycin 49% NA 59% NA Source Résapath 2015 Germap 2012 Résapath 2015 Germap 2012 1 : Strains isolated in 2014 2 : Strains isolated in 2011 3 : Strains isolated in 2010	

Line no.	Stakeholder no.	Comments	Outcome
		4 : Amoxicillin and ampicillin tested respectively in France and Germany References EMEA, 2002. Colistin summary report. EMEA/MRL/815/02-FINAL. EMA, 2014. Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals – Answer to the second request from the EC (ranking of antibiotics) ; Answer to the third request from the EC (new antibiotics) ; Answer to the fourth request from the EC (risk mitigation options) (EMA/381884/2014). EMA, 2015. Concept paper for the development of a reflection paper on the use of extended-spectrum penicillins in animals in the European Union: development of resistance and impact on human and animal health. EMA/CVMP/AWP/37203/2015. GERMAP, 2012. Antibiotika-Resistenz und –Verbrauch. Pilloud M., 1983. Antibiotiques et chimiothérapiques – De la recherche à la pratique. VII. Quelques remarques destinées aux praticiens sur les particularités des polymyxines, des lincosanides, de la spectinomycine, des synergistines, de la bacitracine, de la novobiocine et de la flavomycine. Schweiz. Arch. Tierheilk. 125, 371-382. Prescott J. F., 2000. Peptide antibiotics: Polymyxins, Glycopeptides, Streptogramins and bacitracin. In Prescott J. F., Baggot J. D. and Walker R. D. Antimicrobial therapy in veterinary medicine, Third edition, Iowa State University Press / Ames, USA. Résapath, 2015. Réseau d'épidémiosurveillance de l'antibiorésistance des bactéries pathogènes animales. Bilan 2014.	

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