6 October 2016
EMA/CVMP/185871/2016
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'CVMP strategy on antimicrobials 2016-2020' (EMA/CVMP/209189/2015)

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

Stakeholder no.	Name of organisation or individual
1	Federation of Veterinarians of Europe (FVE)
2	Finnish Food Safety Authority (EVIRA)
3	Alliance to Save Our Antibiotics (ASOA)
4	British Veterinary Association (BVA)
5	European Association of Hospital Pharmacists (EAHP)
6	IFAH-Europe
7	Pharmaceutical Group of the European Union (PGEU)
8	Sustainable Food Trust (SFT)
9	European Group for Generic Veterinary Products (EGGVP)

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	FVE recognises need for a CVMP strategy on antimicrobials for the next years and welcomes the draft paper. We are glad to see that it is recognised the need to take action to improve SPCs and prioritise the use of antimicrobials as well as the need to apply risk proportionate and science based management measures. We also welcome that FVE is recognised as one of the important stakeholders in the field and look forward to work closely with CVMP to improve availability of efficient antimicrobials for use in animals. However we would like to highlight that the strategy is missing reference to • the importance of diagnostics, both to diagnose disease as to do antibiotic sensitivity testing. • illegal sales or import of antibiotics, including Internet sales • antimicrobial resistance risks arising from import of food, travel and trade.	CVMP acknowledges the FVE's comments. We agree on the importance of accurate diagnostics to enable targeted use of antimicrobials and this is highlighted under Aim 5 of the strategy. Although, we also support the other concerns raised (see Aim 6), the strategy is focused on the topics that are priorities for CVMP and fall within the committee's scope for action.
2	New CVMP strategy is welcomed. Deteriorating resistance situation in Europe and worldwide requires active work of everyone involved on the human and veterinary sector so that the efficacy of antimicrobials is maintained and animal and human health are being safeguarded. The work of the CVMP and its expert groups in producing reflection papers, and recommendations on different groups of antimicrobials is acknowledged. Having published the content of reflection papers in international scientific journals is also an	CVMP aims to support the updating of out-of-date SPCs (Aim 3) and availability of effective narrow spectrum antimicrobials (Aim 4). CVMP acknowledges the extensive effort made by professional and livestock bodies, such as FVE and EPRUMA, to provide information to the public on AMR, but does not currently intend to provide its own

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	excellent way to distribute the results of the work done. We see as a major challenge for the MS authorities how all these goals are put into action. Repeatedly there are situation in the MR procedures that out-of-date indications and dosage regimens are seen in the SPCs of generic products. This causes risks for evidence-based and prudent use of antimicrobial products. The situation is very confusing for the practitioners. Currently, the only way to deal with these out-of-date SPCs is referrals. More effort in all Member States should be made to review the products on the market and request the MAHs to update the SPCs. We would also like to address our concern on the availability of necessary antimicrobials. The year 2015 has been extremely challenging for the country relying on narrow-spectrum benzyl penicillin. Weakened availability of narrow-spectrum active substances will have devastating effects on AMR situation. Every effort should be made to keep narrow-spectrum antimicrobials on the market. Finally, it would be of help in informing and educating general public about prudent use and AMR if the CVMP could provide easily understandable information sheets on the topic.	guidance to this specific audience.
3	The CVMP generally does an excellent job of providing accurate assessments of the scientific evidence relating to antibiotics and antibiotic resistance. Furthermore, the CVMP's statement that antibiotics should not be used for routinely, including for the preventative treatment of groups of animals where bacterial disease has not been established in the group/flocks at the time of treatment [1], is strongly supported by ASOA. ASOA also supports the CVMP's position that an overall reduction in antimicrobial use is required, and that this will be best achieved through good husbandry and more targeted use of the medicines (line 114 - line 117).	In collaboration with ECDC and CHMP, the CVMP has provided a categorisation of CIAs for the EC (via the AMEG), see the answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals (EMA/381884/2014). In addition, the AMEG's advice in regards to colistin has been updated in 2016, see the 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

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	However, ASOA believes that the CVMP's recommendations for minimising antimicrobial use and antimicrobial resistance are often too imprecise, and ultimately ineffective. As a result, despite the CVMP's usually accurate analysis of the science, its recommendations have not yet led to significant improvements in farm antibiotic use, although the statement on routine prevention may contribute to such improvements in the future. As recently reported by EFSA and the ECDC, antimicrobial resistance is still on the rise in zoonotic bacteria in the European Union [2]. This is in particular the case for the critically important fluoroquinolones, and for the last-resort antibiotic colistin. Resistance in some infections affecting farm animals is also at a high level in some Member States [3], whereas resistance is much lower in countries using antibiotics more responsibly [4]. The CVMP states in the strategy document that it has "an influential role to play in minimising the risk that AMR presents not only to animal health and consequently to food security, but also to human health" (line 14 - line 16), so it must bear some responsibility for the current lack of progress on these issues in many Member States. A major reason the CVMP's approach has not worked has been because it has failed to sufficiently highlight the clear evidence that intensive, low-welfare husbandry practices are the primary cause of the overuse of antibiotics in farming. As a result, it has been unable to advise on husbandry practices which might reduce reliance on the routine antibiotic use that it opposes. The CVMP has also failed to recognise just how frequently antibiotics are used routinely, without any veterinary diagnosis, in intensively farmed animals. For example, in the strategy document, the CVMP says "It is recognised that group metaphylaxis accounts for a high proportion of veterinary antimicrobial use and in order to support a more reasoned approach the CVMP will endeavour to provide improved SPC guidance about the epidemiological circumstances under which this has shown to be effective and the	(EMA/CVMP/CHMP/231573/2016). It is agreed that CVMP's recommendations should be reviewed as new evidence comes to light in regards to AMR. CVMP recommendations are a combination of general and precise measures, many of the general recommendations have resulted in referrals on AM. Compliance with the recommendations rely on those prescribing the antimicrobials and are difficult to monitor. As an example, the CVMP recommendations on colistin are precise (threshold on mg/PCU of colistin), and will be reviewed to assess its effectiveness, but compliance will rely on measures implemented at national/local level. The CVMP is currently contributing to a joint EMA/EFSA scientific opinion which will review measures that have been taken to reduce the need for, and use of, antimicrobials in animal husbandry in the EU (actions under Aim 2) (RONAFA). This will give consideration to many of the issues identified by ASOA, and extend beyond areas that fall directly within the CVMP's remit, such as husbandry practices. It is anticipated that the Commission will give consideration to the recommendations made in the RONAFA opinion and decide how best to take these forwards. Is not under the CVMP scope to set targets for

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	extent of benefit demonstrated" (lines 118 – 121). There is no mention by the CVMP that group prophylaxis is likely to be even more common than group metaphylaxis. However, a 2012 survey of the Belgian pig industry found that 49 of 50 (98%) farms used group prophylaxis for their fattening pigs, and that 93% of recorded group treatments were purely prophylactic, with just 7% being metaphylactic [5]. Regarding the use of the critically important antibiotics (CIAs), the CVMP has been unwilling to recommend major restrictions on their use, which has had real consequences for human health (see section 1 below). In order to improve future trends, ASOA believes that the new strategy should include an assessment of the effectiveness of key past CVMP actions. Where past CVMP recommendations have failed to result in the desired outcome, new and more effective measures should be considered. Improved recommendations should include not just measures for restricting antibiotic use and improving prescribing, but also measures for improving husbandry and consequently animal health and welfare. ASOA is encouraged the CVMP will be giving further consideration to the importance of the environment in the spread of antimicrobial resistance. The role of the environmental reservoir of resistance genes has often been overlooked, but the most recent research suggests it is highly important and linked with the emergence of resistance in human medicine. Analysis of historic soil archives dating back to 1923 has revealed a clear parallel between the appearance of antibiotic resistance in human medicine and similar β-lactam antibiotic-resistance genes in agricultural soils treated with animal manure [6]. According to the lead author of the research, "The observed bridge between clinical and agricultural antibiotic resistance means we are not going to solve the resistance problem just by reducing the number of antibiotics we prescribe in our GP clinics […] Unless we reduce use and improve stewardship across all sectors – environmental,	reduction of antimicrobial use. Setting targets would be under the remit of the EC. The EC has requested EMA, ECDC and EFSA to set a list of indicators on antimicrobial consumption and resistance, those indicators could in the future be used to set targets by the EC.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	clinical and agricultural – we don't stand a chance of reducing antibiotic resistance in the future" [7]. Finally, the CVMP should consider the implications of new scientific studies showing that very low doses of antibiotics can select for antibiotic resistance. There are now numerous studies showing that selection occurs at concentrations many times below the Minimum Inhibitory Concentration (MIC). These findings mean that the current Maximum Residue Levels in food may be set at inappropriately high levels and should therefore be revised. **Specific recommendations for inclusion in CVMP antimicrobials strategy** ASOA recommends the following points should be considered for the strategy plan: **1. The CVMP should produce new recommendations for restricting the use of critically important antibiotics** The CVMP published a reflection paper on fluoroquinolones in 2007 and one on 3rd and 4th generation cephalosporins in 2009. Because of their importance in human medicine, the reflection papers made recommendations which aimed to prevent these antibiotics being used inappropriately in agriculture. However, these did not include an outright ban on the use of the antibiotics for prevention, nor a ban on their use for group treatments. In particular, the use of the CIAs has not been banned in poultry, as has occurred in the United States. As a result of the CVMP's ineffective recommendations, there has been no reduction in the use of CIAs in EU agriculture. Table 1 shows the sales of CIAs for use in veterinary medicine in the UK.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)

Table 1 Sales of modern cephalosporins and fluoroquinolones in UK veterinary medicine (kg active ingredient) – data from Veterinary Medicines Directorate

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
3rd- and 4th-gen. cephalosporins	220	310	410	410	500	672	739	854	887	976	1,455	1172	1,332	1,189	1,335
Fluoroquinolones	1230	1320	1370	1360	1410	1460	1620	1951	1928	1849	2232	2085	2,434	2,610	2,596
Total critically important	1,450	1,630	1,780	1,770	1,910	2,132	2,359	2,805	2,815	2,825	3,687	3,257	3,766	3,799	3,931

It is clear from Table 1 that the use of CIAs in the UK has been increasing since the beginning of the century and the CVMP's recommended actions have had little or no effect in altering this trend. In 2014, the sales of the CIAs reached another all-time record, the ninth in the last ten years.

The Fifth ESVAC for 2013 [1] also shows (p61) that there has been no reduction in the use of CIAs throughout the EU in recent years.

Increases in the use of CIAs have led to increased levels of resistance, in both farm-animals and humans. In particular, the continuing use of fluoroquinolones for mass medication in poultry in the UK has led to resistance in campylobacter in poultry increasing from 31% in 2013 to 44% in 2014 [8]. In humans, resistance in England

Stakeholder no.	General comment (if any)	Outcome (if applicable)

reached a new record of 48% in 2015 (see Table 2).

Table 2 Resistance to ciprofloxacin in human infections in England (% resistant) [9]

2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
30	30	34	37	37	37	41	43	43	47	48

The levels of resistance in Campylobacter jejuni some other Member States is even higher: according to the recent EFSA/ECDC report on resistance in zoonoses, the average EU level of resistance is now 60% (see p112 of [2]).

In comparison, in the United States where fluoroquinolone use in poultry was banned in September 2005, the level of resistance to the antibiotic in retail poultry meat in 2013 fell to 11%, the lowest level recorded since the FDA began annual testing in 2002 [10]. In 2013, fluoroquinolone resistance in human Campylobacter jejuni infections was just 22% in the US [11]. This significantly lower than in all 13 European countries for which data was reported in the recent EFSA/ECDC zoonosis report (p112 of [2]).

Fluoroquinolones are also commonly used in pig production for treating for treating post-weaning diarrhoea [12], a condition which is favoured by the early weaning of piglets [13][14]. Piglets are weaned early for productivity purposes, as it means the next pregnancy for the sow can be achieved more quickly. It is completely unacceptable that fluoroquinolones are being used merely to increase productivity.

Regarding the use of modern cephalosporins, these antibiotics continue to be licensed for routine dry-cow therapy. Such preventative use of CIAs is wholly inappropriate. Furthermore, although the Summary of Product Characteristics of modern cephalosporin products have been updated to state that the antibiotics should not be used in poultry, this does not constitute an actual ban on their use in poultry.

ASOA asked the UK's Veterinary Medicines Directorate whether modern cephalosporins

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	could still be used in poultry despite the statement on the SPCs and was told: "The Summary of Product Characteristics (SPC) may contain a statement to say the product cannot be used in an animal producing food for human consumption. This does not prohibit its use under the cascade providing the veterinary surgeon understands the risks involved in its use and sets a suitable withdrawal period to ensure that no residues enter the food chain" [15]. ASOA is not claiming that modern cephalosporins are currently being used in UK poultry production, however since such use is not banned, it is perfectly possible that off-label use could recommence again in the future since there is no clear legal impediment to such use. A voluntary ban in 2005 on the use of modern cephalosporins in poultry hatcheries in Quebec led to a fall in resistance in poultry and humans, but in 2007 it was partly reversed leading to increased resistance [16]. Since then, the modern cephalosporin ceftiofur has once again become the most widely used antibiotic in hatcheries in Quebec and a very recent study found resistance to 3rd generation cephalosporins in E. coli from 100% of 82 chicken flocks tested [17]. The CVMP must urgently re-assess its recommendations on the use of CIAs, as they have proven to be ineffective. It should recommend a total on mass medication with CIAs and on the preventative use of these antibiotics. There should be a clear ban on the use of CIAs in poultry. **2. The CVMP should recognise the benefits of extensive, higher-welfare livestock farming and recommend moves in this direction in order to minimize farm antibiotic use** The CVMP states that it believes that an overall reduction in farm antibiotic use is required in order to limit the development of resistance, and that this can be partly	

Stakeholder no.	General comment (if any)	Outcome (if applicable)

achieved through minimising infections through good husbandry.

However, other than mentioning “biosecurity” and vaccination, the CVMP strategy document makes no specific comments on the effects of husbandry methods. Yet, the factual evidence that less intensive farming methods can deliver enormous reductions in the need for antibiotics is completely clear. The CVMP is failing in its duty to make this as explicit as it should be.

According to the EMA, ‘the use of antimicrobial agents in the various animal species varies considerably; for example, the use of antimicrobial agents in extensive production systems, e.g. sheep and goats, is generally relatively low’ (bold added) [18]. It is also known that ‘the highest usage of antibacterial agents among food-producing animals is generally in pigs’ [19]. An exception to this last rule can be the use of antibiotics in intensively farmed veal calves, which can even exceed the use in intensively farmed pigs.

The differences between the usage levels can be extremely high, see Table 3. In the UK, sheep have by far the highest Population Correction Unit (PCU), but the lowest consumption. Pigs and poultry, on the other hand, are the least important species in terms of PCU, but account for an overwhelming majority of usage because they are farmed much more intensively.

Table 3 Sales of antimicrobials for use in farm animals in the UK in 2014 (tonnes active ingredient) and population correction units [8]

Exclusively for	Pigs and poultry	Cattle	Sheep	Multispecies
PCU	1787	1731	About 2700	-
Sales of antimicrobials	308	13	<1	46

Thank you for this comment. The current methodology to assess the effects of residues with antimicrobial activity to the intestinal microbiota, involves a range of options including *in vivo* and *in vitro* studies. The harmonised approach is laid down in a VICH guideline

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Antibiotic use in high-consuming species, like pigs, can be very significantly reduced if the animals are farmed in more welfare-friendly ways. In Denmark, although antibiotic use in pigs is generally significantly lower than in many other Member States, use per 100 animal days is about 10 times lower in organic pigs than in intensively farmed pigs [20]. This shows that the potential benefits in terms of reducing farm antibiotic use of more extensive production are far greater than the gains which can be obtained through merely focusing on biosecurity or vaccination. The CVMP should be explicitly recognise the clear benefits of extensive livestock production, and should also recommend improvements in husbandry practices, like later weaning of piglets, which help minimise disease problems. It is particularly important that, as an impartial scientific committee, that the CVMP make these facts clearly known. **3. The CVMP should consider the implications of new research on sub-MIC doses of antibiotics for setting MRLs** Numerous studies published in recent years have found that doses of antibiotics, which are well below the Minimum Inhibitory Concentration, have the potential to select for antibiotic resistance [21][22][23][24][25][26][27]. Selection at subinhibitory doses occurs not just in vitro, but in vivo as well [28][29]. In addition to selecting for pre-existing antibiotic resistance, subinhibitory doses can induce genome changes which result In antibiotic resistance [30], promote the horizontal gene transfer of multiple antibiotic resistance elements [31], and induce biofilm formation [32][33]. The MIC is the lowest concentration of an antimicrobial which kills or inhibits the growth of the bacteria and it has generally been assumed that selection for resistant bacteria	and applied in the USA, Japan and the EU, and likely in Canada and Australia/New Zealand. In the context of the establishment of CODEX MRLs, the JECFA applies a similar approach. The information provided in your comments will need further consideration by the CVMP. Any possible future changes in methodology will require further discussion in international context.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	only occurs between the MIC of the sensitive bacteria and the higher MIC of the resistant bacteria. Were this assumption to be correct, then concentrations lower than the MIC of the susceptible bacteria would not be selective. However, Swedish scientists have shown this not to be true. They examined several antibiotics and found that at concentrations well below the MIC of the susceptible bacteria, resistant bacteria grew faster than sensitive bacteria, which means that the antibiotics remained selective at these concentrations [21]. They determined a Minimum Selective Concentration (MSC) above which the antibiotic exerted a selective pressure in favour of resistant bacteria. For the Salmonella stains examined, the MSC of streptomycin and tetracycline were found to be respectively just 1/4 and 1/100 of the corresponding MICs. For E. coli, the MSC of ciprofloxacin was either 1/10 or 1/230 of the MIC, depending on the resistance mutation. Similar findings on selection for resistance at sub-MIC doses have been reported in other studies [22][23][24][25][30][27], and it has been found that at doses 150 times below the MIC, tetracyclines can promote the horizontal transfer of resistance genes into E. coli [31]. Scientists point out that environmental concentrations of antibiotics at sub-MIC concentrations could be selecting for resistance, and that selection could also be occurring through residues in food. A review article published by Nature stated that: “the consumption of meat or milk that has been contaminated with antibiotics in quantities that are below the detection limit, could result in antibiotic concentrations in the body that are above the minimal selective concentration, which could lead to the enrichment of resistant bacteria” [26]. The current method for setting Microbiological Acceptable Daily Intake (ADI) for antibiotics, which can be significant in determining Maximum Residue Limits for various animal tissues, assumes that selection in the human gastrointestinal tract only occurs at	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	the MIC and higher concentrations. This, for example, is the case for the Microbiological ADI of the fluoroquinolone enrofloxacin. The CVMP's summary report on this issue finds that E. coli is the most sensitive species to enrofloxacin, and a MIC50 for E. coli is used in setting the Microbiological ADI [34]. This turns out to be lower than the toxicological ADI and is therefore used for setting the various MRLs, which are set at a level such that the CVMP calculate that the consumer intake of the antibiotic via residues will not exceed 74% of the Microbiological ADI [35]. However, the principal metabolite of enrofloxacin is the human antibiotic ciprofloxacin and, as mentioned above, the E. coli MSC of ciprofloxacin is between 10 and 230 times lower than the MIC, depending on the resistance gene. The MSC of enrofloxacin will almost certainly also be much lower than the MIC used in the summary report. This means that consumer intake of residues from the consumption of meat will in fact, in some cases, result in concentrations in the gastrointestinal tract which are well above the MSC, and therefore in selection for resistant bacteria. ASOA believes that the CVMP needs to re-evaluate the current assumptions regarding antibiotic resistance selection and promotion of resistance genes transfer at sub-MIC concentrations. It has generally been concluded that little or no selection of antibiotic resistance occurs in the human gut as a result of antibiotic residues in food, so long as residues are below the MRL. It is now clear that the scientific assumptions behind that conclusion are false. Re-assessment of MRLs should lead to lower residues being required in many cases, and therefore longer withdrawal periods. **4. The CVMP should consider the benefits of setting targets for reducing farm antibiotic use**	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	The Review on Antimicrobial Resistance (the O'Neill review) appointed by the Prime Minister of the UK, David Cameron, published a report in December recommending that targets be set for reducing farm antibiotic use to a set level per kg of livestock and fish. ASOA supports the use of targets, as these have proved to be successful in countries like the Netherlands and Norway which have reduced their use of farm antibiotics to much lower levels than in many other Member States. However, ASOA believes that targets should be set by species, so that there is a set level (perhaps the same level) in each farm species. This will require antibiotic use data by species to be collected. ASOA also believes that separate targets should be set for the critically important antibiotics, and these should require a rapid and very large overall reduction. The Netherlands has shown that extremely large reductions in the use of the CIAs can be achieved in a short space of time: between 2011 and 2013, the sales of fluoroquinolones for use in veterinary medicine was cut by about 72% and the sales of modern cephalosporins by about 98.5% [36]. By 2014, less than 0.5kg of modern cephalosporins were used in the four main Dutch farm-animal species (pigs, cattle, chickens and turkeys), demonstrating that most use of these antibiotics in European farming is unnecessary and avoidable. ***References*** [1] Question and answer on the CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005), 9 October 2014 [2] EFSA and ECDC, 2016, The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014 [3] Rugna et al. 2015, Sequence types and pleuromutilin susceptibility of Brachyspira hyodysenteriae isolates from Italian pigs with swine dysentery, Veterinary Journal, 203	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	[4] Pringle et al. 2012, Antimicrobial susceptibility of porcine Brachyspira hyodysenteriae and Brachyspira pilosicoli isolated in Sweden between 1990 and 2010, Acta Veterinaria Scandinavica, 54 [5] Callens et al. 2012, Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds, Prev Vet Med, 106 [6] Graham et al. 2016, Appearance of β-lactam Resistance Genes in Agricultural Soils and Clinical Isolates over the 20th Century, Scientific Reports, 6 [7] Newcastle University press release, http://www.ncl.ac.uk/press/news/2016/02/antibioticresistance/ [8] VMD, 2015, UK VARSS 2014, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477788/Optimised_version_-_VARSS_Report_2014__Sales___Resistance_.pdf [9] Data obtained from Public Health England via a Freedom of Information request [10] NARMS, 2015, Retail meat interim report 2013 [11] NARMS, 2015, Human isolates report 2013 [12] De Briyne et al. 2014, Antibiotics used most commonly to treat animals in Europe, Veterinary Record, 175 [13] Campbell et al. 2013, The biological stress of early weaned piglets, Journal of Animal Science and Biotechnology, 4 [14] McLamb et al. 2013, Early Weaning Stress in Pigs Impairs Innate Mucosal Immune Responses to Enterotoxigenic E. coli Challenge and Exacerbates Intestinal Injury and Clinical Disease, PLoS One, 24 [15] Email from Nick Renn, Head of Legislation at the VMD, to Cóilín Nunan, 16	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	January 2015 [16] Dutil et al. 2010, Ceftiofur resistance in Salmonella enteric serovar Heidelberg from chicken meat and humans, Canada, Emerging Infectious Diseases, 16 [17] Boulianne et al. 2016, Drug use and antimicrobial resistance among Escherichia coli and Enterococcus spp. Isolates from chicken and turkey flocks slaughtered in Quebec, Canada, Can J Vet Res, 80 [18] Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013, Fifth ESVAC report [19] Grave et al. 2010, Comparison of the sales of veterinary antibacterial agents between 10 European countries. Journal of Antimicrobial Chemotherapy, 65 [20] Ministry of Environment and Food of Denmark, http://www.ft.dk/samling/20131/almdel/flf/spm/495/svar/1156714/1401964.pdf [21] Gullberg et al. 2011, Selection of Resistant Bacteria at Very Low Antibiotic Concentrations, Plos Pathogens, 7 [22] Gullberg et al. 2014, Selection of a Multidrug Resistance Plasmid by Sublethal Levels of Antibiotics and Heavy Metals, MBio, 5 [23] Liu et al. 2011, Selective Advantage of Resistant Strains at Trace Levels of Antibiotics: a Simple and Ultrasensitive Color Test for Detection of Antibiotics and Genotoxic Agents, Antimicrobial Agents and Chemotherapy, 55 [24] Hughes and Andersson 2012, Selection of resistance at lethal and non-lethal antibiotic concentrations, Current Opinion in Microbiology, 15 [25] Sandgren 2014, Selection of antibiotic resistance at very low antibiotic concentrations, Uppsala Journal of Medical Sciences, 119	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	[26] Andersson and Hughes 2014, Microbiological effects of sublethal levels of antibiotics, Nature Reviews Microbiology, 12 [27] Jørgensen et al. 2013, Sublethal ciprofloxacin treatment leads to rapid development of high-level ciprofloxacin resistance during long-term experimental evolution of Pseudomonas aeruginosa, Antimicrobial Agents and Chemotherapy, 57 [28] McVicker et al. 2014, Clonal expansion during Staphylococcus aureus infection dynamics reveals the effect of antibiotic intervention, PLOS Pathogens, 10 [29] Pereira et al. 2014, In vivo selection of resistant E. coli after ingestion of milk with added drug residues, PLOS One, 9 [30] Chow et al. 2015, Potential impacts of aquatic pollutants: sub-clinical antibiotic concentrations induce genome changes and promote antibiotic resistance, Frontiers in Microbiology, 6 [31] Jutkina et al. 2016, An assay for determining minimal concentrations of antibiotics that drive horizontal transfer of resistance, The Science of the Total Environment, 1 [32] Mlynek et al. 2016, Effects of Low-Dose Amoxicillin on Staphylococcus aureus USA300 Biofilms, Antimicrobial Agents and Chemotherapy [33] Hathroubi et al. 2015, Sub-inhibitory concentrations of penicillin G induce biofilm formation by field isolates of Actinobacillus pleuropneumoniae, Veterinary Microbiology, 179 [34] CVMP 1998, Enrofloxacin, Summary report (2) [35] CVMP 2002, Enrofloxacin, Summary report (5) [36] Data from the SDa publications at	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	http://www.autoriteitdiergeneesmiddelen.nl/en/publications	
4	1. The British Veterinary Association (BVA) is the national representative body for the veterinary profession in the United Kingdom and has over 15,000 members. Our primary aim is to represent, support and champion the interests of the veterinary profession in this country, and we therefore take a keen interest in all issues affecting the profession, including animal health and welfare, public health, regulatory issues and employment matters. 2. We are grateful to have the opportunity to respond to the European Medicines Agency (EMA) consultation regarding the Committee for Medicinal Products for Veterinary Use (CVMP) strategy on antimicrobials 2016-2020 and supports the CVMP's vision of the availability of effective antimicrobial medicines for the treatment of infectious diseases of animals with, at the same time, minimum risks to animals or humans arising from their use.	Comments acknowledged.
5	In general, it is encouraging and welcome that the CVMP has developed a strategy on antimicrobials 2016-2020 which in part represents improvement on that which went before. However, as healthcare professionals on the frontline of the battle against antimicrobial resistance in the human health sector, EAHP would like to see further ambition in the strategy, including outlines of how the success or not of the strategy will be evaluated and if necessary adjusted during the 4 year period. We suggest a mid point review in 2018. We further suggest the strategy include active monitoring and assessment of the extent to which CVMP guidance on the responsible use of antimicrobials in animals is being communicated, read and acted upon. In relation to the Strategy's ambition to follow a "One Health" approach and work with	Thank you for your suggestions. CVMP agrees that it would be valuable to have a review of progress against the strategy and it is probable that this will be done mid-way through the period addressed. The effectiveness of some of the CVMP's past measures will be reviewed under the RONAFA, but it may take several years before the results of many of the actions can be seen. The EMA/CVMP activities on AMR are actively discussed and shared with colleagues dealing with public health within the EMA and with other EU institutions as ECDC, EFSA and the CRL AMR.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	relevant stakeholders, we suggest relevant aspects of CVMP activity be more regularly included within the liaison activity EMA conducts with its healthcare professional and patient/consumer working parties. CVMP should also understand the potential global impact of its guidance and other AMR-focused activity, in terms of providing international leadership. Give the global dimension of AMR, best practice work in the area, such as new CVMP guidance or methodologies, should be actively promoted internationally in order that other systems may draw lessons and inspiration. This should be reflected more fully within the ambitions of the 4 year strategy.	The EMA/CVMP activities on AMR are increasingly been publicised, as an example, some of the EMA/CVMP considerations on classes of antimicrobials are now published in scientific journals. The EMA/CVMP is increasing its participation at international fora, e.g. OIE, Codex Alimentarius, AGISAR and TATFAR. The EMA/CVMP regularly provides input to the EC on subjects related to regulation and use of antimicrobials.
6	The opportunity for the Industry to comment on this draft CVMP strategy is welcomed. It provides some clarity on the overall strategy concerning antimicrobials and addresses among others not only the antimicrobial resistance discussion but also animal welfare and the availability of effective antimicrobials. It is acknowledged that the CVMP addresses not only new antimicrobials but also existing and long established antimicrobials in its strategy for the following years. But a well-balanced and reasonable approach needs to be chosen to warrant safe and efficient antimicrobials for the use in veterinary medicine. For the development of new antimicrobials data requirements need to be predictable, reasonable and assessable whereas existing antimicrobials need to be addressed in a proportionate well-balanced way including Industry as well as authorities. IFAH-Europe understands some of the measures proposed in the CVMP policy as there is a scientific rationale. However, the additional regulatory burden and/or obstacles that are proposed will have a major impact of future antibiotic development. It will be important for CVMP to keep development costs in mind when future guidelines are proposed i.e. on environmental risk. Also, perhaps the CVMP should mention that given these new measures could further hamper the development of new antimicrobials,	The CVMP supports development of new and existing antimicrobial VMPs where this is in line with responsible use principles and endeavours that regulatory requirements are proportionate and science-based. CVMP considers that there are sufficient scientific grounds to make a reasonable assumption that reducing antimicrobial use will result in a reduction of AMR, and agree that this should be achieved through encouraging responsible use. The strategy supports responsible use throughout. We agree that animal welfare should not be sacrificed in order to decrease antimicrobial use and the strategy advises that this should be achieved through a holistic approach including use of vaccination, husbandry measures and improved biosecurity (Aim 3).

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	some other steps need to be taken by the EU to ensure future development. IFAH-Europe supports responsible use, however the strategy of the CVMP seems to consider only decreased use, and whilst responsible use may lead to a decrease in use, the focus on decrease sets a dangerous precedent, as the treatment of animals should not be compromised or endangered and a policy of just decreasing use could lead to such an outcome.	
7	The PGEU would like to ask for clarification if the term "antimicrobials" includes endoparasiticides, as in some Member States these products are safely supplied over-the-counter in pharmacies by a pharmacist. (line 386-387)	In the context of this document, “antimicrobial” follows the OIE definition “Antimicrobial agent”: *“means a naturally occurring, semi-synthetic or synthetic substance that at in vivo concentrations exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms). Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition”* (http://www.oie.int/eng/normes/mcode/en_glossaire.htm#rubrique_definitions) Although addressing coccidiostats is not a direct objective of the CVMP strategy, some of them have broader antimicrobial properties
9	EGGVP is concerned about antimicrobial resistance and, recognising the importance of setting appropriate and sustainable measures, it very much welcomes and fully supports the CVMP strategy on antimicrobials 2016-2020, in particular the following aspects: • Interdisciplinary approach, covering all areas that may help reducing and controlling AMR	The CVMP envisages that based on this strategy (Aims 2 & 6) we will be working closely with colleagues in human medicine. This has already come about through the work of the AMEG on the categorisation of the CIAs, and will continue as CVMP considers the categorisation of the aminoglycosides and extended expectrum-penicillins, and in future risk assessments.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	• Scientific approach, which is crucial at a moment when political awareness and opinion are increasing. Measures applied to VMPs should be proportionate and evidence-based. • GLOBAL approach / international actions necessary • Acknowledgement that greater transparency and predictability for companies considering antimicrobial product development is necessary • Acknowledgement that the greatest driver of AMR in people is the use of antimicrobials in human medicine As a general comment, EGGVP believes that more emphasis/focus should have been given to the need for a One Health approach. During a recent evaluation of the Commission Action Plan against AMR (RAND Europe, Nov 2015), conclusions were that more progress had been made in AMR issues related to animal health (such as appropriate use of antimicrobials, prevention of infections and their spread, development of alternative treatments, monitoring and surveillance, and education and training of animal health professionals) than in the corresponding human health issues. Overall, this CVMP strategy is considered a very positive step. However, EGGVP understands this is a high level document and areas of work are not described in detail. For this reason, many items described below by EGGVP are presented also as additional “general comments”.	The CVMP is also addressing the topic of AMR in the environment. See Aim 2.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 12-16	2	**Comment:** The sentences are quite difficult to understand, thus breaking down into different sentences is proposed. **Proposed change:** This objective is threatened by the challenge of antimicrobial resistance (AMR**). Therefore,** by providing guidance to ensure the responsible use of antimicrobials in animals, the CVMP has an influential role to play in minimising the risk that AMR presents not only to animal health and consequently to food security, but also to human health.	Text amended.
Lines 24-26	2	**Comment:** We agree that the role of antimicrobial usage in the resistance development in bacteria originating from companion animals should be seen increasingly important. **Proposed change:** None.	Noted.
Lines 40-43	1	**Comment**: It should be mentioned that the main objectives of the revision of the Directive are to increase the availability of veterinary medicinal products, to reduce the administrative burden on enterprises, to improve the functioning of the internal market for veterinary medicinal products and to fight antimicrobial resistance. Increase the availability of all veterinary medicines	Partly accepted. The text refers directly to the wording used in the Explanatory Memorandum for the proposed Regulation. It is already stated in the Introduction to the strategy that a key objective of CVMP is to promote the availability of effective antimicrobial VMPs in order to protect animal health and welfare. Text adjusted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		should be one of the key priorities, which will ensure animal health and welfare and public health risks including antimicrobial resistance. It should be highlighted that any measure to be taken especially with regard to banning of certain antimicrobials from use in animals, should by proportionate, seen under the One Health approach and must follow an appropriate risk assessment. Even when good management is followed thoroughly, it will happen that animals may get sick sometimes. It is of ultimate importance that when that happens we could be able to control any disease and prevent from its spread in other animals and humans. **Proposed change**: Add: *The objectives of this proposal are to increase the availability of veterinary medicinal products, to reduce the administrative burden on enterprises, to improve the functioning of the internal market for veterinary medicinal products and to fight antimicrobial resistance.* This proposal contains provisions that aim to strengthen the benefit-risk assessment for antimicrobial veterinary medicinal products, *strengthen controls around their use under the cascade and* provide a legal tool to preserve certain antimicrobials for human use *if seen the need to do so ~~and strengthen controls around their use under the cascade~~, while ensuring that efficient antimicrobials will be available for the treatment of all animals and proportionate measures apply to both human and*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		veterinary sector.	
Lines 42-43	7	**Comment:** The PGEU supports the use of a legal tool to preserve certain antimicrobials for human use. **Proposed change:**	Noted. This is supported by CVMP under Aim 2.
Line 45	5	**Comment:** EAHP puts on record its support for the referenced 2014 recommendation by EMA/AMEG to the European Commission for the categorisation of human critically important antimicrobials with guidance on the level of restriction that should be placed on their use in veterinary medicine in order to limit the risk to public health. We urge the CVMP to follow up that the recommendation is sufficiently acted upon.	Comment acknowledged. CVMP is currently preparing reflection papers for Aminoglycosides and Extended-spectrum penicillins and will provide recommendations for the categorisation of these substances.
Lines 47-49	7	**Comment:** The PGEU supports the recommendation that new antimicrobials used in veterinary medicine should be accompanied by a reinforced risk assessment taking into account the risk to public health. **Proposed change:**	Noted.
Lines 49; 297-299	6	**Comment:** The meaning of *'reinforced risk assessment'* should be clarified: The risk assessment has to be well-balanced, proportionate and manageable especially since the CVMP acknowledges later on the following (297-299): *'Investigating a link between antimicrobial usage in animals and AMR in humans is hindered by the complexity of transmission routes and ecological aspects of the selection pressure for resistant bacteria'*	Noted. This will be addressed in the CVMP's Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food (EMA/CVMP/AWP/706442/2013).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 54-56	1	**Comment**: It is important that effective antimicrobials are available for the treatment of any infectious disease in animals **Proposed change**: The CVMP's vision is ***to ensure*** the availability of effective antimicrobial medicines for the treatment of ~~***important***~~ infectious diseases of animals ~~***with***~~ ***while***, at the same time, ~~***minimum***~~ ***minimising the*** risks to animals or humans arising from their use.	Accepted; although some infections could be addressed through management and husbandry changes.
Lines 54	4	Comment: We question use of the word important in this context; it implies that an animal suffering from reduced health and welfare from a common or unimportant infectious disease would not require treatment with antimicrobials. **Proposed change:** Delete important	Accepted.
Lines 54-55	6	**Comment:** The 'important infectious diseases of animals' should be clarified on. What qualifies an infectious disease to be important? E.g. Economically expensive or animal welfare largely affected if no treatment can be provided?	Taking account of comments received, "important" has been deleted.
Lines 54-55	6	**Comment:** The preceding CVMP strategy on antimicrobials (2010-2015) specifies the vision as: "The CVMP strategy seeks to promote the continued availability of effective antimicrobials for use in animals whilst at the same time acting to <u>minimise risks</u> to animals or man arising from their use". In the new	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		version the term “minimum risks” is used instead. Please revert to the earlier wording i.e. “minimise risks”. **Proposed change:** *“**The CVMP’s vision is** the availability of effective antimicrobial medicines for the treatment of important infectious diseases of animals ~~with,~~ **whilst** at the same time, **minimising risks** to animals or humans arising from their use”.*	
Lines 61-63 Lines 194-197 Lines 228-233	9	**Comment:** When considering the prohibition of use of a certain antimicrobial in veterinary medicine, the CVMP should take a balanced and interdisciplinary approach taking the following into consideration: Animal health and welfare: lack of effective and appropriate alternatives will result in serious availability problems in treating serious diseases, which will result in animal suffering and high mortality. Public health: if alternatives to the banned antimicrobial appear to be worse as per their contribution to the increase of resistance Environment: if available alternatives to the prohibited product are more detrimental for the environment. **Proposed change**: Lines 197-197 Further to this, the CVMP agrees that specific human critically important antimicrobials which are of last resort for treatment of life-threatening disease in humans should be excluded from veterinary use where this measure is supported by the findings of an assessment of the hazard and consequences to human	Partly accepted. The text has been simplified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		health, **and where alternatives exist in veterinary medicine that do secure a positive risk balance for the treatment of sick animals and their welfare, the protection of the environment as well as public health.**	
Line 62	1	**Comment**: Antimicrobial resistance is a multifactorial problem, where all mechanisms are not well known. However it is well acknowledged that all living organisms are involved (i.e. humans, animals and environment) and therefore it is important to approach the antimicrobial resistance problem through the holistic One Health approach. **Proposed change**: …transfer of antimicrobial resistance from animals to humans ***and vice versa as well as from interaction between humans, animals and the environment***, and…	Partly accepted. The text has been amended to emphasise the One Health approach.
Lines 64-69	2	**Comment:** Surveillance of usage data is very important. However, we find collecting these data at the moment on large scale quite tedious and too costly as there are no automatic systems available to do so. The wording of the aim 3 is somewhat weak although we understand that the CVMP has limited powers to act on areas other than reviewing existing MAs. The role of the CVMP could be, however, more active. For instance, statements or guidance	Noted. We prefer to keep the text here brief. Please also note

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		could be given to promote the need for actions. **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 **encouraging prudent use of existing products and updating marketing authorisations and if not done so by MAHs.** 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.	that Aim 5 relates to prudent use.
Lines 70-71	1	**Comment**: **Proposed change**: …to encourage the development of ***new veterinary medicinal products, including antimicrobials and alternatives to antimicrobials, and improve the way the existing ones are used***, especially…	Partly accepted. Amendment made.
Lines 70-72	4	**Comment:** **BVA strongly supports this statement.** **Proposed change:** **We consider it essential to encourage the development of**	Comment acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		new and existing antimicrobial veterinary medicinal products, especially in order to fill therapeutic gaps and for minor uses and minor species, and to foster the development of effective alternatives to antimicrobials.	
Lines 70-72	6	**Comment:** The support for the development of new and existing antimicrobial veterinary medicinal products is acknowledged. But Industry needs clarity especially on the existing antimicrobials: A task force with representatives from the Industry as well as from authorities is proposed to address the divergence between the proposed re-development and widening of indications for well-established antimicrobials on the one hand and the proposed referral procedures on the other hand. For new indications (or sometimes merely to keep old indications) new data packages including dose finding and determination studies and therefore residue studies might need to be conducted.	Noted.
Line 71	6	**Comment:** Besides filling therapeutic gaps, an aim should be to keep several treatment options for each indication due to the risk of resistance development if only a single antibiotic drug is registered for an indication and used in the field. **Proposed change:** *"… medicinal products,* ***to keep several treatment options for each indication and*** *especially in order to fill …"*	In this section the Aims are summarised. An amendment has been made to the detailed Aim 3.
Line 73	1	**Comment**: Replace '*antimicrobials'* by *'veterinary medicinal products,*	Not accepted. The focus is on antimicrobials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		including antimicrobials'. **Proposed change**: … responsible use of ***veterinary medicinal products, including*** antimicrobials both in accordance…	
Line 74	1	**Comment**: The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) provides veterinarians acting within a veterinarian-client-patient relationship (VCPR) with greater prescribing and dispensing options so that animals can receive the medications when needed. This is critical given the relatively few numbers of drugs labelled for use in animals. **Proposed change**: …under the cascade. *Investigate the setting up of a system similar to 'AMDUCA' system in United States in order to stimulate the development of veterinary medicines for MUMS and to put in a framework off-label use.*	This is for the Commission to address under the new Regulation.
Line 75	1	**Comment**: Recognising the One Health aspect and actively promote it. **Proposed change**: Aim 6: Recognising that AMR is a global ***One Health*** problem affecting both animal	Accepted.
Line 76	5	**Comment:**ECDC and EFSA appear to EAHP as critical agencies	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		for the CVMP to liaise and coordinate with. It is therefore worth providing their explicit mention within Aim 6. **Proposed change:** "European Commission, **European Centre for Disease Prevention and Control, European Food Safety Authority**.."	Accepted . Amendment made.
Lines 75-78	2	**Comment:** The list of partners should also include regulatory authorities in the Member States. **Proposed change:** … in partnership with the European Commission, **competent authorities in the Member States,** international regulatory bodies, human and …	Accepted. See also amendment under Aim 6.
Line 77	5	**Comment:**Provision should be made within Aim 6 to licence CVMP to work with stakeholders from the human health sector, such as healthcare professionals. **Proposed change:** "livestock industries, **and other relevant stakeholders**"	Human health organisations are already mentioned, no amendment necessary.
Line 81	4	**Comment:** **Missing word/typo**	Corrected. Thank you.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: **Guideline for the demonstration of efficacy of veterinary medicinal products containing.**	
Lines 84-85	2	**Comment:** metaphylaxis and prevention – The text on prevention needs to be further considered taking into account the decisions taken regarding on draft Veterinary medicines regulation. **Proposed change:** None at this point	Noted. In this case, reference is made to the definitions in the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).
Lines 87-93	2	**Comment:** One health approach is strongly supported. The importance of good co-operation between human medicine and veterinary medicine expert is vital in combatting antimicrobial resistance. Especially the resistance in zoonotic pathogens requires this co-operation. **Proposed change:** None	We agree.
Lines 90-93	1	**Comment**: FVE is very supportive of proportionate and science-based risk management that recognises the need for taking more action and applying responsible use practices in human medicine as well.	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change:	
Lines 90-93	4	**Comment:** BVA strongly supports this statement. We consider it essential that risk management measures applied to VMPs should be proportionate and evidence-based. **Proposed change:**	Comment acknowledged.
Lines 93-95	6	**Comment:** We welcome the constructive spirit of these strategic points; however, regulatory uncertainty will remain since new guidance does not provide a clear path, since the outcome of risk assessments is left to "expert judgement" rather than being defined by transparent criteria. Therefore, development of a new antibacterial for use in animals in Europe still entails an unacceptably high risk for companies that still have an active discovery pipeline, since the outcome of the assessment remains unpredictable. This, coupled with the failure of the current business model (as in human medicine) shifts the focus towards products other than antibacterials. **Proposed change:** focus on greater predictability when elaborating guidance on AMR hazard characterisation and risk assessment is absolutely required if the hope expressed in line 93 is to become true.	Noted. Work on the CVMP's Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food (EMA/CVMP/AWP/706442/2013)
Lines 94-95	6	**Comment:** The wording *'lack of regulatory uncertainty'* does not make sense. The issue is the current regulatory uncertainty, we would suggest deleting 'lack of' to improve the meaning. **Proposed change:** *development and address the ~~lack of~~*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"regulatory uncertainty" that has been identified as a contributor	
Lines 97-101	1	**Comment**: *The scope of this sentence should be wider, i.e. supports also the development of alternatives, such as vaccines, etc. and diagnostic tools.* **Proposed change**: The CVMP supports the development of new antimicrobial VMPs ***and other alternatives, such as vaccines***; however, in order to slow the development of antimicrobial resistance resulting from over-reliance on single substances, a range of antimicrobial ~~***agents***~~ ***substances*** should ideally be available for use in veterinary medicine. This means that substances that are already authorised must be used sustainably and the conditions of use provided in the SPC***, including the need for sensitivity testing,*** should support this. …	Partly accepted. Support for development of vaccines is noted in former lines 122-123. Reference to susceptibility testing is now made directly in former line 117.
Lines 99-101	2	**Comment:** The importance of supporting sustainable use of new products should also be highlighted here. **Proposed change:** This means that **both substances that are already authorised and new products must be used sustainably and the conditions of use provided in the SPC should support this**.	Accepted. Amendment made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 100-106 Lines 278-289 Lines 318-323	9	**Comment:** The continued availability of a wide range of effective antimicrobials not only at the human but also at the veterinary side is of vital importance. The CVMP should note that for the old molecules the requirements arising from referrals could result in considerable research effort by many companies that would be put into developing and updating dossiers. Many products could disappear since the intention of industry to invest is such 'old' products may not be very high. Also think how this could have an impact re. pain and distress of farm animals for carrying studies. EGGVP would like to invite CVMP to consider the following actions: • To anticipate availability problems, i.e. by means of impact assessment, especially to see the potential effect on the number of products, and impact in animal health and welfare and finally for human health and food supply. • To consider a general framework for dialogue with stakeholders during a referral procedure when a large number of companies is involved. Today there are initiatives from industry to collaborate between MAHs concerned by a referral to generate the data. This approach is sensible, but creates significant practical difficulties and having open dialogue between stakeholders and CVMP would be seen as a positive step. **Proposed change:**	Comments acknowledged. CVMP has the intention to collaborate with the relevant stakeholders regarding the process for SPC harmonisation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 103-106	6	**Comment:** This approach in itself undermines the CVMP's own guidance, and contributes to companies refraining from investments in existing antibacterials, knowing from experience that at any point in time changes can be made to the SPC regardless of data generated by the companies.	The comment is acknowledged; however, CVMP needs to consider options for achieving SPC harmonisation as foreseen in the proposed VM Regulation. The text has been amended.
Lines 111-113	2	**Comment:** Based on the recently published information on colistin, MCR-1 resistance revision of reflection paper (EMA/755938/2012) should be reviewed. Perhaps this could be added here. **Proposed change:** The CVMP will continue to address emerging AMR issues and, following the recommendations of the AMEG, risk profiling will now be undertaken for the **extended-spectrum penicillins** and **aminoglycosides and existing document on colistin will be revisited**.	This review has now been completed by the AMEG (see http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211080.pdf).
Lines 111 and 125	5	**Comment:** The extent to which the AWP, AMEG, ITF, and ADVENT provide full multidisciplinarity in their composition and advice is unclear to EAHP. Representation of the human health aspect is important in respect of the 'One Health' approach and EAHP therefore trusts the CVMP will ensure this necessary breadth of advice and input is received by CVMP through the duration of the strategy. This is important in respect to many issues, including, but not limited to, tendencies in the animal sector to use some medicines intended for human use on an off label	Noted. The AMEG includes representatives from ECDC and CHMP, and there are also AWP members with a background in human healthcare. ITF is a multidisciplinary group that includes scientific, regulatory and legal competences. ITF can provide a discussion platform for early dialogue with applicants taking into account both human and veterinary aspects. The ADVENT group may call upon expertise from the human domain as required. The CVMP is working

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		basis.	increasingly in a One Health context.
Lines 114-115	6	**Comment:** This sentence is speculation in the absence of substantial scientific evidence. There is ample evidence that when an antimicrobial is used 'on label' the level of resistance to that antimicrobial remains low both in target pathogens and foodborne/commensal bacteria. Refer to CEESA publications for AMR monitoring data on both target pathogens and foodborne/commensal bacteria **Proposed change:** Suggest removing this sentence	CVMP considers that this sentence can be supported based on data that are beginning to emerge and recent ecological studies linking antimicrobial use and AMR.
Lines 114-115	7	**Comment:** The PGEU supports the reduction in antimicrobial use as a measure to limiting expansion of AMR. **Proposed change:**	Noted.
Lines 114-118	9	**Comment:** This paragraph should emphasise on the importance of responsible use as a crucial measure to combat AMR, as highlighted in lines 381-382. The reduction of use only should not be the target, but it should be seen as an intrinsic beneficial consequence of appropriate use. **Proposed change:** It is probable that one of the most effective measures to limit expansion of AMR is an overall reduction in antimicrobial use, **in line with responsible use principles**. This is best achieved through measures to prevent infections from establishing (husbandry, biosecurity, vaccination, etc) and more targeted use of antimicrobials where it is still necessary to guard animal	Not accepted. It is clear from the following text that reduction in use is to be achieved by following responsible use principles.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		health (e.g. by use of accurate **examination and** diagnosis, **supported by sensitivity testing wherever possible,** evidence-based regional treatment guidelines and correct dosing regimens).	
Lines 114-121	3	**Comment:** Most farm antibiotic use is in low-welfare intensive systems. **Proposed change:** There are very large differences in the need for antibiotics according to the husbandry methods used. Most antibiotics, and a large majority of group treatments, whether prophylactic or metaphylactic, are in intensive farming systems. In order to achieve the reductions in antibiotic use that are needed, moves to less intensive systems will be required. This will include later weaning for piglets and greater access to the outdoors for all animals.	The influence of husbandry systems on preventing infections and thereby the need to use antimicrobials is noted in the strategy (aims 1 and 3). and will be addressed in the RONAFA report
Line 115	1	**Comment:** **Proposed change:** …reduction in antimicrobial use **in both human health and animal health sector**.	The context of this paragraph is CVMP's role in reducing and refining use of antimicrobials in animals.
Lines 115-118	2	**Comment:** From the experience, we would add to the measures guiding antimicrobial usage via legislative actions which take into	Not accepted. Non-legislative measures have also been effective.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		account national resistance situations. **Proposed change:** This is best achieved through measures to prevent infections from establishing (husbandry, biosecurity, vaccination, etc) and more **targeted use** of antimicrobials where it is still necessary to guard animal health (e.g. by use of accurate diagnosis, evidence-based regional treatment guidelines and correct dosing regimens **and use of legislation to restrict or prohibit the usage**).	
Line118	2	**Comment:** "group metaphylaxis". From the communication point of view the term metaphylaxis is extremely challenging in non-English country. It would help to have definitions available. **Proposed change:** Please, add the footnote to provide the definition of metaphylaxis	Accepted.
Lines 118-121	3	**Comment:** It is likely that group prophylaxis represents a higher proportion of antibiotic use in intensive farming systems than group metaphylaxis. **Proposed change:** Add text which recognises that group prophylaxis is likely to represent a very large proportion of farm antibiotic (see [5]) and a statement that the CVMP will endeavour to ensure that group prophylaxis is ended throughout the EU.	The text under Aim 1 has been amended, in reference to oral formulations: "…it is also recognised that a high proportion will be for **prevention or** metaphylaxis of disease **in groups of animals**." A further amendment has been made: "Systematic preventive use of antimicrobials should be phased out as soon as possible".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 118-121	6	**Comment:** It would be helpful if CVMP could clarify which data/criteria will be at the basis of this improved SPC guidance.	This will be based on the data requirements for metaphylaxis claims as outlined in the revised Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1)
Lines 119-120	1	**Comment:** We need the development of more and better diagnostic tools to support veterinarians on their diagnosis and selection of the appropriate antimicrobial. **Proposed change:** …in order to support a more reasoned approach the CVMP will endeavour **to encourage the development of accurate and** easy to use diagnostic tools and to provide improved SPC guidance about the epidemiological circumstances under which this has shown to be effective and the extent of benefit demonstrated..	Although CVMP encourages the development and use of accurate diagnostics, it does not regulate these products so cannot take direct action to stimulate their development.
Lines 124-125	6	**Comment:** The establishment of the Innovation Task Force (ITF) and the CVMP Ad Hoc Group on Veterinary Novel Therapies (ADVENT) providing guidance for novel therapies to the MAH is greatly appreciated.	Comment acknowledged.
Line 126	4	**Comment:** In line 126 the strategy recognises the value of the cascade to allow treatment of diseases for minor uses and minor species	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		(MUMS). However, we would like to reiterate the current everyday importance of the cascade in all species to allow access to the most appropriate antibacterial –especially with reference to comments below regarding narrow spectrum antibacterials and possible further restrictions on access to potentiated amoxicillin. Given the increasingly prescriptive wording of summaries of product characteristics (SPCs) we believe that in the absence of a wide range of veterinary medicinal products animals cascade must be retained. **Proposed change:** The CVMP recognises the value of the cascade **to allow for the treatment of diseases where there is no medicine authorised in the UK for a condition and** to allow treatment of diseases for MUMS…	Accepted with slight modification.
Line 129	4	**Comment:** It is our understanding that veterinary surgeons in farm animal practice wishing to adhere to responsible use of antimicrobials guidance must use the cascade to prescribe a narrow spectrum antibiotic where a fully licenced antibiotic exists. BVA supports the development of older, narrow spectrum products to reduce use of the Highest Priority CIAs which includes 3/4G Cephalosporins, Fluoroquinolones and Macrolides. **Proposed change:**	Comment acknowledged. Thank you.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 129-130	1	**Comment:** Older, narrow spectrum formulation of Category 1 could need reduce the use of critically important antimicrobials, however other aspects of those products, like the longer withdrawal periods, may have cost implications that should also be considered. Harmonisation of SPCs for those Category 1 products could be however very helpful. Additionally we could not see how the use of Category 1 antimicrobials could reduce the off label use. **Proposed change:** older, narrow 129 spectrum Category 1 (lower risk)5 antimicrobials for treatment of common indications could more generally reduce the use of critically important antimicrobials ~~**and off-label use**~~ that results solely due to the access and easier	Agreed. The intention is to address the scenario outlined by the BVA above, but it is agreed that this was not conveyed in the text. The sentence has been amended as proposed in the comment, and in the strategy under aim 4.
Lines 129-134	6	**Comment:** This offer for support is appreciated; however, the current business model – including the lack of protection of technical documentation – is counterproductive to such major investments.	Noted.
Lines 132-134	1	**Comment:** *CVPM should go further and find ways to promote the development of Category 1 products as well as of alternatives and diagnostics for all species including MUMS, whether or not*	Noted, however the CVMP has to use its resources efficiently within its scope and capabilities.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the industry shows interest. **Proposed change:** ~~***Where interest is shown by industry, t***~~ ***T***he CVMP, in conjunction with its various working parties, will provide advice to facilitate development of such products as well as those for MUMS/limited markets.	
Lines 132-134	6	**Comment:** It is not enough to facilitate development of new antimicrobials or to develop new formulations of existing products. The incentive has to extend out to better IP and patent life. For the development of '*modern formulations*' of older narrow spectrum antimicrobials a more general scientific advice regarding data requirements (e.g. residue studies, dose evaluation) is also needed. See also comment to 284-289. **Proposed change:** Modify sentence to include the possibility of patent extension and IP protection	The proposed changes are outside of CVMP's scope.
Lines 146-154	6	**Comment:** It is not clear how this guideline should be interpreted for a completely new antibacterial. This guideline works from a basis of "first line, second line" antibacterials. This is contradictory to the more recent AMEG-advice which in section 3.4 states the following: "*For this reason, the EMA/CVMP/CHMP/AMEG cannot recommend the EC to create detailed guidelines on what substance to use as "first line", "second line" or "last line" medication for certain animal infections in the EU. EU Member States (MSs) could be encouraged to develop such detailed guidelines taking into account among other information the general categorisation*	Not agreed. In our view the Guideline can be applied consistent with the AMEG's advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		presented in this document." Hence, an approach as given in this guideline is not valid at an EU level anymore. It would be impossible to deal with all new antibacterials as if they were "second line", certainly those which would fill existing treatment gaps. **Proposed change:** The guideline will need to be revised to be in compliance with the recommendations of the AMEG-advice	
Lines 155-161	1	**Comment:** *FVE welcomes that the need for metaphylaxis to minimise the consequences on herd health from diseases which are highly contagious and severe is recognised and agrees that on having in place guidance on study design for claims for* ***metaphylaxis and prevention*** *of disease.* **Proposed change:**	Noted.
Lines 155-166	2	**Comment:** It is not easy to understand the difference between metaphylaxis and prevention. **Proposed change:** Please, add footnote to the definitions	Accepted. Footnotes included.
Lines 165	6	**Comment:** 'risk is very high and the consequences are severe' is unclear. We would also consider that not treating if the risk is low but the consequences are severe may not be acceptable or easy to implement. **Proposed change:** Replace "and" by "or".	Not accepted. This strategy does not intend to provide such level of detail – the topic will be addressed further in the RONAFA report.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Further elaborate on 'very high' and 'severe consequences'	
Lines 163-165	3	**Comment:** **Proposed change:** Preventative treatment of groups of animals where no disease has been diagnosed in any of the animals should be prohibited.	Antimicrobials should only be used preventively where there is knowledge of the pathogen which represents a risk and the antimicrobial to which it is likely to be susceptible. Partly accepted. Amendment made.
Lines 163-166	4	**Comment:** BVA supports the use of antimicrobials, in exceptional cases, to prevent disease from developing where a vet has diagnosed a high risk of bacterial infection in the herd/flock at risk. It is the imperative of the veterinary surgeon to uphold animal welfare and whilst we agree that antimicrobials should never be used to compensate for the impact of husbandry systems or a lack of biosecurity it is counter to the responsibilities of a veterinary surgeon to stop their use to prevent disease that is predictable. **Proposed change:**	Comment acknowledged.
Lines 165-166	2	**Comment:** The same is true for metaphylactic use as for preventive use. Antimicrobials should never be used to compensate for the impact of husbandry systems or a lack of biosecurity. The text should be revised to take this into account. **Proposed change:** Antimicrobials should never be used ~~**preventatively**~~ to	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		compensate for the impact of husbandry systems or a lack of biosecurity.	
Lines 169-175 to be added to Proposed Actions	3	**Comment:** A large amount of recent scientific evidence has shown that antibiotics can select for resistance at concentrations which are just a small fraction of the MIC **Proposed change:** The CVMP will re-assess MRL levels and withdrawal periods in the light of the new scientific evidence showing that antibiotic resistance can be selected for at concentrations which are a small fraction of the MIC.	Thank you for raising this issue. Please refer to the response on this topic in the general comments section of the document.
Lines 169-175 to be added to Proposed Actions	3	**Comment:** The CVMP's recommendations on the use of the CIAs have not resulted in a reduction in use across the EU. **Proposed change:** The CVMP will re-assess its recommendations for limiting the use of the fluoroquinolones and modern cephalosporins. It will recommend ban on the use of these antibiotics for mass medication and for all preventative use, including in individual animals.	It may be too early to assess the impact of CVMP's recommendations as it takes time for them to be implemented into product information, but it should be noted that they have been used as the basis for measures taken in certain member states. CVMP has the possibility to review its recommendations as new evidence becomes available.
Lines 174-175	9	**Proposed change:** We will provide training to **applicants (industry) and** assessors in the application of CVMP guidance documents relating to antimicrobial VMPs.	CVMP does not usually provide training to industry, but provides Scientific Advice and individual members have provided presentations at conferences on an ad hoc basis. Workshops/focus group meetings have been

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			organised with stakeholders to address specific technical issues.
Lines 188-190	2	**Comment:** It seems that because the referral so far has concerned only 3rd- and 4th-generation cephalosporins administered systematically, the use of these should be limited only where there are no alternative. We consider that the same principle should be applied to the local treatment (e.g. intrammaries). **Proposed change:** whilst those in Category 2 (higher risk) which includes fluoroquinolones and ~~**systemically acting**~~ 3rd- and 4th-generation cephalosporins, should be used only where there are no alternative antimicrobials authorised for the given species and indication.	Not accepted. This is based on the AMEG categorization and CVMP/SAGAM risk profiling of 3rd and 4th generation cephalosporins (EMA/CVMP/SAGAM/81730/2006).
Line 194	4	**Comment:** BVA supports the exclusion of EMA/CVMP Category 3 products (last resort for treatment of life-threatening disease in humans) from veterinary use except in exceptional circumstances – there may be cases where it is appropriate to treat an infection in a companion animal for the benefit of the people in the household – e.g. TB/ MRSA – I accept an argument could be made for euthanasia but we think that safeguards could be put in place to ensure that this is retained for exceptional use. **Proposed change:**	Comment acknowledged. These situations should be taken into account in the risk assessment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 194-197	1	**Comment:** When making any decision for restricting the use of a certain substance for human use only, should carefully take into account the risks to animal health and veterinary public health as well. Failure to control an infection to animals can easily lead to spread of disease to more animals, other animal species or humans. **Proposed change:**	Noted. It is expected that most of these substances are not yet authorised for use in veterinary medicinal products and decisions may need to be made before a clear role in veterinary medicine is identified. The text has been modified.
Lines 206-209	6	**Comment:** This definition of acceptable risk is so vague that it does not provide any guidance at all. It is clear for e.g. carbapenems (which is a political, not a scientific assessment since so far, the science indicates that any transfer seems to be happening from the human setting to animals, not vice versa). It is totally unpredictable for a new substance. **Proposed change:** Clarification and specification of the criteria leading to an acceptable risk would be helpful to make the outcome of an assessment less arbitrary and more predictable.	This should be addressed further in the Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013), rather than in this high level document.
Lines 206-213	1	**Comment:** FVE strongly supports this approach. **Proposed change:**	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 210-213	2	**Comment:** Although the principle of basing risks upon robust scientific evidence is agreed to, one cannot forget precautionary principle. It is too late to act once resistance factors are widely spread. Therefore, actions to protect the efficacy of last resort antimicrobials in the treatment of human infections should be a priority. The matter is complicated. Resistance situations vary in Member States. There should be room for national actions – especially if the good resistant situation is to be maintained. **Proposed change:** None.	Noted.
Lines 214-218	1	**Comment:** *European Union has developed high standards on the use of antimicrobials and livestock production in order to control antimicrobial resistance including the risks of foodborne infections by resistant bacteria. However imported food from third countries of animal origin has not been always produced with the same high European Standards and thus may lead to import of certain types of resistant bacteria.* *As regards direct transfer of AMR, it is true that this is going both directions (see CALLISTO report)* **Proposed change:** …types of resistant bacteria; ***import of food of animal origin from third countries that have not been produces***	Not accepted. This issue is sufficiently addressed under Aim 6 (final sentence).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		according to the high European standards may also lead to import of certain types of resistant bacteria to the European Union. ***~~however,~~*** ***tT***he CVMP recognises that close contact between companion animals and their owners also offers an opportunity for direct transfer of AMR ***from animals to their owners and vice-versa,*** about which there is currently limited knowledge. A reflection paper	
Line 218	5	**Comment:**Recommendations need to be assessed as to whether they have been acted upon. **Proposed change:** add "The extent to which the recommendations have been acted upon will be assessed in 2016".	Not accepted. See proposed actions. Beyond this, we do not currently have resources to commit to this assessment.
Line 220	1	**Comment:** **Proposed change:** …recognised. Use of antimicrobials in animals ***and plants***, including in aquaculture	Accepted.
Lines 220-221	6	**Comment:** In the assessment the risk of human contamination should not be dismissed. There is evidence of antimicrobials being found down-steam of hospitals and prisons in the USA. **Proposed change:** Include human environmental contamination	Accepted.
Lines 228-249 to be added to	3	**Proposed change:** The CVMP will develop a reflection paper on the impact of	See above, lines 169-175.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Proposed Actions		subinhibitory doses of antibiotics and the consequences for MRLs an withdrawal periods.	
Lines 230-231	7	**Comment:** The PGEU supports the establishment of a list of antimicrobial substances which should be reserved for treatment of human infections only. **Proposed change:**	Noted.
Line 232	6	**Comment:** It is impossible to understand how the list will be established, since there is no definition of a one health approach. **Proposed change:** Add a clear definition or explanation of what constitutes “a one health approach” to the document.	Amended: “This will involve collaboration with the human medical sector”.
Lines 232-233	2	**Comment:** Besides taking One Health approach into account the different resistance situations in Member States should also considered. More restrictive list may be needed in those Member States having less resistance problems, thus there should be room for national actions **Proposed change:** To be added: In addition Member States are encouraged to establish more restrictive lists of their own taking account their resistance situation and patterns of antimicrobial usage.	CVMP assumes that the list of substances reserved for treatment of human infections only, as foreseen in the proposed Regulation on VMPs, will be developed at EU level. CVMP supports development of recommendations at regional level, also (e.g. treatment guidelines) but would prefer to keep the emphasis in this strategy document on CVMP’s actions.
Lines 238-241	2	**Comment:** The need for guidance for companion animals is agreed to. The treatment of them differs greatly from that of production	Comment acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		animals. For instance, the threshold for treatment is lower as there is no need to take MRLs and withdrawal periods into account. Also the cost of treatment is not affecting factor and there generally is very close owner-animal contact. **Proposed change:** None.	
Line 239	5	**Comment:**More than consider **Proposed change:** "the CVMP **will** develop further guidance for industry on the assessment of the risk to public health from antimicrobials intended for companion animals" [i.e. delete and replace "will consider" to "will"]	Not accepted. CVMP cannot commit to developing this guidance until experience is gained with the draft guidance for VMPs for food-producing species.
Lines 242-243	2	**Comment:** Please, take into account the comment for lines 111-113 on colistin resistance. **Proposed change:** Please, add colistin review to this action point.	Acknowledged. The AMEG has provided an updated risk-profiling for colistin (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).
Lines 242-243	6	**Comment:** It would be helpful if the CVMP could follow the approach as outlined in the GL on the assessment of the risk to public health from AMR due to the use of these products, when undertaking the risk profiling. That by itself would contribute to the experience referred to in lines 238-241.	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 244-246	3	**Proposed change:** Add after the sentence: "This will include an examination of the extent to which more high-welfare, extensive farming systems can contribute to reducing the need for antibiotics"	This will be addressed in the EMA/EFSA RONAFA report, but is not under direct remit of CVMP.
Line 247	5	**Comment:**EAHP supports the proposal of reflection paper on the role of AMR in the environment and the feasibility of addressing this in the environmental risk assessment for veterinary medicinal products. However, EAHP suggest weight would be added to this activity by conducting it jointly with DG Agriculture. **Proposed change:** "The CVMP will develop **in conjunction with DG Agriculture a** reflection paper to consider the role of AMR…"	CVMP will aim to take a One Health approach and consult with relevant EU Agencies during the public consultation phase. No amendment made.
Lines 247-249; 223-226	6	**Comment:** There is no need for a reflection paper to consider the role of AMR in the environment unless there is an established risk regarding the relevance of AMR in the environment for the overall AMR. This would also answer the question regarding the feasibility of an assessment. Unless there is a need the assessment is not feasible, time consuming and expensive. Therefore in general it is proposed that first of all a real risk is identified by the CVMP before the drafting of a guideline and an assessment for each substance/product is put into force as a new requirement. As discussed elsewhere in the document (223-226) the CVMP itself acknowledges that the risk of the contribution of AMR in the environment should be further	The sentence has been amended. The further clarification is accepted but it is not felt necessary to include it.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		substantiated *'The cycling of these resistance genes between the different ecosystems is extremely complex and requires further research. The CVMP acknowledges that further consideration should be given to the contribution of veterinary antimicrobial use to the environmental resistome.'* **Proposed change: *'**The CVMP will develop a reflection paper ***whether there is a need*** to consider the role of AMR in the environment and the feasibility […]. ***This would only need to be considered if a relevant risk can be identified (taking into account the recommended use patterns, e.g. condition of use in the aquaculture).***'*	
Line 249	1	**Comment:** *We suggest that CVMP looks also into the development of a reflection paper on assessment of the imported risks of antimicrobial resistance, such as import of food, travel of people and animals, trade of goods, etc.* **Proposed change:** *Add an item* ***CVMP will develop a reflection paper to consider the role of imported food and other factors, such as travel of people and animals and trade, on the development and spread of AMR in the European Union.***	Although we acknowledge this problem, CVMP has to focus resources on those areas where it can have most impact, and that are within its scope.
Line 249	8	**Comment:** We only became aware of this consultation this evening so only have time to make one rushed comment. We recommend that the CVMP develop a reflection paper on the	CVMP agrees that this is a very interesting topic and that it would be valuable to have the findings of further research available in the public domain.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		potential to reduce the incidence of antimicrobial resistance AMR) in farm animals if data were available to practitioners on the relative depletion rates of AMR to each antimicrobial in each livestock species for which products are licensed. As the CVMP will know, legal withholding periods for antimicrobials are based on residues depletion studies with the aim of ensuring that residues fall below the Maximum Residue Limits for various tissues, calculated to stay below the Acceptable Daily Intake based on typical human diets. As a result, some antimicrobials, for example some cephalosporins products used in cattle and a pleuromutalin used for laying hens, have zero withholding periods because residues never exceed the MRL. However, it is not known what level of AMR is induced by the products nor how the levels of resistance to these antimicrobials decline in key indicator bacteria. Research at Bristol University by Delsol and others with enrofloxacin and avilamycin showed that a relatively short increase in the withholding period for pigs resulted in a very large decline in AMR. We believe that additional research could show that resistance to some antimicrobials declines much more quickly than to others, and that were such data to be established by additional research, funded, we would suggest by the licence-holding pharmaceutical companies, this would provide veterinarians and farmers with the information to make more informed choices, especially were antimicrobial treatment	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		is required in the days, weeks or months prior to slaughter, or in the case of eggs where currently either a zero withholding period or slightly longer withholding period are required, based entirely in residues depletion and with no consideration of the decline in resistance. We realise there will be situations, such as the treatment of disease in broiler chickens with chlortetracycline, where studies have shown that resistance in key indicator bacteria persists beyond the average lifetime of the animals, even when the birds are treated when young. This could be the case with all antimicrobials, but until such research is undertaken it is not possible to state this with certainty, and it could be that resistance to some antimicrobials will decline more quickly than to others. With pigs, cattle and other species with longer life spans there would be greater opportunity to select products with resistance declines to match expected slaughter dates. Our suggestion is that if such information were available it should not, initially at least, be used to increase legal withdrawal periods, but simply be made available as an additional tool to help practitioners make informed choices that might help to reduce the burden of AMR in some bacterial species. **References** *Delsol et al 2004*. 'Emergence of fluoroquinolone resistance in the native	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Campylobacter coli population of pigs exposed to enrofloxacin. JAC 53:872-874 *Delsol et al 2011.* Persistence of a wild type Escherichia coli and its multiple antibiotic-resistant (MAR) derivatives in the abattoir and on chilled pig carcasses, International J of Food Microbiology, 140: 249-253 *Delsol, Anne,* Research Project Final Report, for Defra, 'Antimicrobial resistance: an evaluation of risk factors to identify control strategies. Defra Project Code OD2015 **Proposed change (if any):**	
Lines 250-251	1	**Comment:** **Proposed change:** *Change in* Take measures to ensure ***~~continuing~~ availability and*** effectiveness of authorised veterinary antimicrobials	Partly accepted.
Line 253	6	**Comment:** Effective antimicrobials not only have a role for animal welfare, healthy livestock and a quantitative food supply but also on the safety of the food produced and public health, where zoonoses are concerned. **Proposed change:** *'and ensure healthy livestock**, a healthy food supply and (veterinary) public health'***	Agreed. Proposal partially accepted.
Lines 254-256	6	**Comment:** We welcome CVMP's support for such programmes. Industry will continue to run the four CEESA programmes. In	The CVMP strongly supports the establishment of harmonised approaches for target pathogens monitoring

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		addition, we would encourage CVMP to support the initiative from HMA, led by Prof. P. Borriello, to establish a harmonised approach for target pathogen monitoring in the EU, in a more active way towards the Commission, not only from a scientific but also from a funding perspective. It has been clearly stated that co-funding by Industry (as initially proposed) is not acceptable.	in the EU.
Lines 258-262	2	**Comment:** Perhaps, encouragement to develop methods could be added here instead only stating the current situation. **Proposed change:** Therefore, for new antimicrobial substances the marketing authorisation holder should be encouraged to have in place plans to monitor the **evolution of susceptibility in target pathogens,** including sampling based on a scientifically determined protocol and susceptibility testing using standardised methodology (where available). **Development of standardised methodology should be enhanced and encouraged.**	Accepted. Proposal amended slightly.
Lines 258-262	9	**Comment:** This paragraph refers to new antimicrobial substances, although it is included under chapter "3. Take measures to ensure continuing effectiveness of authorised antimicrobials". It should be clarified if the plans to monitor the evolution of susceptibility would apply to new antimicrobials or to already	A further sentence has been added: "Development of improved and standardised methodologies for new and existing antimicrobials is encouraged."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		existing ones.	
Line 259	5	**Comment:**More than encourage **Proposed change:** "for new antimicrobial substances the marketing authorisation holder should be **required** to have in place plans to monitor the evolution of susceptibility in target pathogens" [i.e. delete and replace "encouraged" to "required"]	This would be a change to current data requirements that is not explicitly foreseen in the new Regulation of Veterinary Medicinal Products, in addition the CVMP cannot envisage if plans would be needed for all new antimicrobials.
Lines 259-260	6	**Comment:** The MA holder should not be expected to conduct AMR in target pathogens on an annual basis. In fact it is unlikely that there should be any significant shift in the MIC with a 12 month period **Proposed change:** Define a suitable period between susceptibility testing	This topic is for future discussion and it is not appropriate to include this level of detail in a high-level strategy document..
Lines 275-277 Lines 327-330	9	**Comment:** In 2015 VetCAST was formed with the aim to provide scientifically-based definition/approval veterinary-specific breakpoints. It is anticipated that these data will be of value for informed prescribing as well as for monitoring susceptibility. **Proposed change:** Lines 327-330 The CVMP will consider the potential benefits to veterinarians and to animal health of routinely establishing veterinary clinical break-points for antimicrobials **and will cooperate with**	Not accepted. Arrangements with VetCAST are still under discussion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		VetCAST on definition and approval of breakpoints for new and existing veterinary antimicrobials. CVMP will consider the practical arrangements, the potential impact on data requirements and the implications for new and existing marketing authorisations.	
Line 281	5	**Comment:**More than should **Proposed change:** "These products **will** be addressed by scientific re-assessment"	Not accepted. CVMP cannot commit to review all these products within the timescale of this strategy.
Lines 284-289	6	**Comment:** In the context of re-developing existing narrow spectrum antimicrobials further consideration *'MUST'* be given to '*developing methods to review dosage regimes and for subsequent adjustment of withdrawal periods in order to avoid loss of species, indications…'.* This consideration should include incentives, minimum acceptable data packages for existing, well established antimicrobials which in consequence should be accepted by all authorities, concepts to refine the dose and the applicable withdrawal period (WP) maybe without the need to conduct new studies (e.g. by taking into account the Target Animal Safety studies for increasing the dose or by considering a safety span for the WP). **Proposed change:** *'Further consideration **must** be given to developing methods to review dosage regimens **preferably without conducting new studies** and for subsequent adjustment of withdrawal periods in order to avoid loss of*	Accepted with slight modification to proposed text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		species and indications from older antimicrobial products during such procedures.'	
Lines 289-292	2	**Comment:** **combinations of antimicrobial substances**, especially if these include critically important antimicrobials, are always of particular concern. Combinations including CIAs should be the highest priority in the referrals. These kinds of "shotgun" products have damaging effect for the reputation of animal production and veterinary medicine and do not take forward prudent use principles in combatting AMR. Please, consider making referrals for products containing combinations of antimicrobials including CIAs a priority e.g. combinations containing colistin. **Proposed change:** Please, consider adding the following: **Products containing combinations of critically important antimicrobial substances including colistin should be addressed by scientific re-assessment.**	The CVMP has addressed the colistin combinations under a recent referral and fluoroquinolone combinations have been voluntarily withdrawn from the market. The CVMP aims to prioritise referrals for antimicrobial VMPs, where procedurally possible. No amendment necessary.
Line 292	6	**Comment:** mass medication is not precise. **Proposed change:** replace mass medication by group medication.	Accepted.
Lines 293-295	2	**Comment:** We understand that the scientific committee considers that risk mitigation measures for antimicrobial VMPs should be based on scientific risk assessment and that they should be proportionate and that any potential negative impacts on animal health and	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		welfare must be taken into account. We, however, wonder if this is taking actions far enough. It is not clear what is meant by "negative impacts" here. When taking into account differences in resistance situation in different geographical areas and considering also public health it is necessary to broaden the perspective. Interests may contradict each other when considering that AMR is zoonotic and affect public health when antimicrobials are used in animals. It is clear that compromises are necessary when public health is part of the equation; precautionary principle needs to be considered, too. **Proposed change:** The negative impact to public health should be added to the text. In addition it should be remembered that antimicrobial resistance will also have a major negative impact on animal health and welfare when no efficacious antimicrobials are available i.e. sometimes it may be necessary to kill/slaughter the animals carrying resistant organisms causing disease in order to prevent the dissemination of resistance and ensure the welfare of other animals.	Accepted. Amendment made.
Lines 297-298	6	**Comment:** A concrete model must be established for the assessment of a possible connection/correlation between antimicrobial usage in veterinary medicine and AMR in humans before the requirements for veterinary medicinal products are further increased leading to loss of substances and consequently therapeutic gaps.	Comment noted, but there is sufficient evidence (e.g. JIACRA[1], ECDC/EFSA report[2]) of a connection between antimicrobial usage in veterinary medicine and AMR in humans to justify making the assessment of the risk.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/01/WC500181485.pdf
[2] EFSA Journal, 14(2):4380

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 301-302	6	**Comment:** As we indicated in the general comments, decreased usage as a goal is difficult to accept. We could support responsible use instead. **Proposed change:** The CVMP therefore supports responsible use that should lead to a decreased usage of antimicrobials	Noted. CVMP supports the aim to reduce overall use through responsible use, as expressed here.
Lines 301-306	2	**Comment:** The goal to reduce the overall consumption of antimicrobials is strongly supported: However, it could be mentioned that the best way to reduce the consumption of antimicrobials in animals is to reduce the need of antimicrobials in animals. **Proposed change:** Please, consider addressing the idea mentioned in the comments.	We consider that it is clear in the text that prevention of disease in order to reduce the reliance on antimicrobials is a goal (lines 302 to 306).
Lines 308-309	2	**Comment:** It is important that possible geographic areas have different resistance situations. Therefore, it is important that when assessing the data on the susceptibility of target pathogens these data are representative for whole Europe. **Proposed change:** The susceptibility data should be representative throughout all the members because of the differences in resistance situation in different Member States.	Partly accepted. Requirements pre-authorisation are laid out in the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).
Line 310	5	**Comment:**More than consider	This is dependent on the text of the new Regulation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: "The CVMP will develop methods for post authorisation data to be provided and reviewed [i.e. delete and replace "will consider" to "will develop methods"]	
Lines 310-313	2	**Comment:** Regarding post-authorisation issued in general we wonder if there is a need to encourage reporting more actively lack of efficacy as suspected adverse drug reaction. Now only the practitioner will note that the treatment was not efficacious. Very seldom this is reported. **Proposed change:** Please, consider adding the following: **Reporting of the lack of efficacy (by practitioners) should be encouraged.**	Accepted. Amendment made under Aim 3: "Veterinarians should also be encouraged to report cases of suspected lack of efficacy due to antimicrobial resistance via the pharmacovigilance system."
Lines 312-313	6	**Comment:** Which criteria will be used will be applied to this assessment, and what could be possible outcomes? History has taught us that AMR will appear sooner or later, and is present in target pathogens for currently existing substances. Although the rates of resistance are still relatively low for many drug/bug combinations, these are expected to increase – which thresholds would trigger re-evaluation? On the other hand, there are cases where the resistance rate as determined *in vitro* is high but where the products are still showing clinical efficacy in the field.	This topic is for future discussion and it is not appropriate to include this level of detail in a high-level strategy document.
Lines 314-315	1	**Comment:**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		It is recognised that the variations in the amounts of antibiotics used in the different member states could be a result of the use of other authorised medicinal products, e.g. zinc oxide. ESVAC should consider collecting data on such indicators that would allow for a more accurate interpretation of the results. *Additionally, FVE would like to raise awareness about the use of coccidiostats and suggest to consider monitoring of their use as well.* **Proposed change:** …data on ~~***antimicrobial***~~ consumption (sales and use) ***of antimicrobials and other relevant substances such as Zinc oxide, as well as of coccidiostats*** under **ESVAC** and	The ESVAC project has considered collecting data on zinc oxide and although encourages MSs to collect such data, considering its dual use as a VMP and as a feed additive, and that the substance is a mineral, has decided not to collect data on its use for the time been. Coccidiostats with antibacterial activity (ionophores) are almost solely used as feed additives which are outside the scope of ESVAC.
Line 319	6	**Comment:** *' … where there is evidence that there may be '* is a contradiction **Proposed change:** *….where there is evidence that ~~there may be~~* ***<u>of</u>*** *a change in the …..*	Accepted.
Lines 321-323	6	**Comment:** The researching and developing Industry clearly opposes the aim of harmonising SPCs for active substances. Different formulations of the same product might have a huge impact especially on the pharmacokinetic profile (and consequently on the efficacy in the target tissue and the WP). This paragraph is opposed by the expressed wish of the CVMP to support the re-formulation of old antimicrobials. If subsequently	Comment noted. The process of SPC harmonisation is under discussion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		SPCs are harmonised anyway the Industry has no return of investment at all to do so! In consequence a SPC harmonisation would oppose the re-development of old antimicrobials. The referral procedures should therefore have a defined scope which cannot be -from a scientific as well as investment point of view- to adapt SPCs to the minimum common denominator.	
Lines 309; 327-Line 330	6	**Comment:** The *'data on the susceptibility'* and the criteria to assess the susceptibility as well as the institution(s) establishing '*veterinary clinical break-points'* should be clearly defined.	Agreed. The strategy identifies the need for standardisation of susceptibility testing and interpretive criteria.
Lines 327-330	6	**Comment:** CVMP should take into consideration the VET02-A3 (formerly M37-A3) procedure of CLSI for establishing clinical breakpoints in order to arrive at a globally harmonised approach of setting clinical breakpoints. **Proposed change:** Include reference to CLSI VET02-A3 in the strategy paper	This level of detail is not appropriate for a strategy document. Further comment is given in the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).
Line 328	4	**Comment:** It is unclear what clinical break-point means. **Proposed change:** Define clinical break-point.	Footnote included.
Line 330	1	**Comment:** *FVE suggests that CVMP should look into developing an opinion of how to increase availability of veterinary diagnostics throughout the EU. For this purpose we need to consider establishing Diagnostic Market Stimulus (DMS) pots to overcome the mismatch between the cost and benefits of*	Economic aspects are not within the remit of CVMP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		diagnostics as suggested in the latest Jim O'Neil report. **Proposed change:** *Add an item* ***CVMP will develop a reflection paper to stimulate the use of diagnostic tools and to overcome the mismatch between the cost and benefits of diagnostics.*** ***CVMP will develop a reflection paper to consider the establishment of a regulatory framework for veterinary diagnostic tools and susceptibility testing.***	However, we support the development and use of rapid diagnostic tests as a means to improve targeting of antimicrobial use and to reduce unnecessary use (Aim 5). A new action has been proposed.
Line 332	1	**Comment:** **Proposed change:** …products, ***including antimicrobials,*** especially for minor uses and minor	Change not necessary.
Lines 336-338	2	**Comment:** More discussion is needed how new antimicrobials against infections caused by multi-resistant bacteria are used in treatment of animal patients. Here stakeholders' proposals are stated but in the CVMP strategy there is clear need to take into account disease prevention and public health considerations, too. Some cases eradication of pathogen from animal population could be most efficacious way to reduce antimicrobial treatment. Companion animal pathogens such as MRSP are problematic. MRSP is capable to obtain/develop resistance factors quite easily and the development of new antimicrobials will solve the	ADVENT is proposed to provide advice on development of "novel" therapies, including alternatives to antimicrobials, not new antimicrobials. We agree that it is important to maintain the efficacy of antimicrobials – this is addressed in Aims 3 and 5.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		problem with MRSP only temporarily. The key point is what the effect on human health is when treating the animal when AMR or bacteria are transferred to human. Now the work of ADVENT is given as an alternative. **Proposed change:** The development of new antimicrobials is only a small part of the solution and attention should be paid also on how the efficacy of these antimicrobials could be maintained as long as possible.	
Lines 349-357	6	**Comment:** One has to realise that dose optimisation, addition of a species and/or indication requires investments similar to the development of a new product, and fully equals this in case new formulations are also involved in the effort. Specific protection of technical documentation similar to new products could provide an incentive; it is completely unattractive to make these investments only to have (cheaper) copies on the market a few years later. Also, one should realize that such efforts do not provide long-term solutions as for all compounds currently in use, resistance mechanisms are established within target pathogen populations and with a restricted therapeutic arsenal (as a consequence of referral procedures), selection pressure is expected to increase. In addition, some of these are probably already used under the cascade, hence the impact on medicines availability might be over-estimated.	Comment noted.
Lines 349-352	7	**Comment:** The PGEU supports the commentary that there could be an opportunity to develop new formulations of older	Comment acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		category 1 narrow spectrum antimicrobials for use in veterinary patients in order to reduce the use of critically important antimicrobials. **Proposed change:**	
Lines 356-357 Lines 376-378	9	**Comment:** The CVMP should note that the current EC proposal for regulation on veterinary medicines does provide incentives for new marketing authorisations only (protection of technical documentation for every new species added). In EGGVP's view, rewarding and protecting all major investments in existing products (new dosage, new species including minor species, new pharmaceutical forms, new routes of administration, new withdrawal period or new indication with significant clinical benefit) would be beneficial for the competitiveness of the whole industry (generics and originators), by promoting an innovative and dynamic development of veterinary medicines industry in Europe.	Comment noted.
Lines 363-365	9	**Proposed change:** Provide regulatory guidance through the Innovation Task Force and ADVENT group, and scientific advice on request from marketing authorisation applicants on the development of new antimicrobial products**, new formulations of older Category 1 narrow spectrum antimicrobials** and alternatives to antimicrobials for the treatment of microbial infections	Accepted.
Line 365	5	**Comment:** Assessing extent to which strategic actions are	Thank you for this suggestion. It may be too soon to

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		working is imperative **Proposed change:** Add new action “Assess the extent to which regulatory guidance through the Innovation Task Force and ADVENT group is being effective in the development of new antimicrobial products”.	assess the effectiveness of this action in the timeframe of the strategy.
Lines 366-369 Line 367	4	**Comment:** BVA supports the development of novel vaccines as alternatives to antimicrobials, but would like to highlight the necessity for more effective vaccines for the control of major population diseases. Whilst vaccines that reduce lung lesions may have welfare and economic benefits, they often do not perform well enough to replace the need for additional antimicrobial use. Additionally, vaccines are often used to combat viral disease and these are not directly of benefit to reduced antibiotic usage. Vaccines have to be carefully targeted according to local circumstances. Only limited numbers of vaccines can be used in any given group of animals as the SPC states they must not be used within two weeks of administration of any other vaccine. **Proposed change:** giving particular attention to vaccines**, both novel and improved versions of those currently available,** as part of the current…	Partly accepted. Text amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 366-369	2	**Comment:** ¨The CVMP's aim to reflect further on measures that could be taken to promote the development and access to market of alternatives to antimicrobials, giving particular attention to vaccines is fully supported. There has been lots of problems on availability of poultry vaccines during last year. **Proposed change:** None.	Comment acknowledged.
Line 370	5	**Comment:** More than consider **Proposed change:** "The CVMP will develop a list of minor uses and minor species indications for which there are currently therapeutic gaps and for which development of antimicrobial or alternative products should be encouraged". [i.e. delete and replace "will consider" to "will"]	Not agreed, the CVMP needs to consider resources before committing to a task.
Line 376	1	**Comment:** **Proposed change:** …CVMP will ***take actions to*** support expanding of indications…	Not accepted. In terms of new indications, interest/data first has to be provided by industry.
Lines 386-387	7	**Comment:** The PGEU would like to ask for clarification if the term "antimicrobials" includes endoparasiticides, as in some Member States these products are safely supplied over-the-counter in pharmacies by a pharmacist.	This strategy does not apply to endoparasiticides (see comments above).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change:	
Line 387	1	**Comment:** **Proposed change:** …on veterinary prescription ***prescribed by a veterinarian.***	Accepted.
Lines 388-390	2	**Comment:** We fully support the development and implementation of evidence-based national and regional treatment guidelines. All SPCs should be up-to-date. As stated in general comments we see as a major challenge in the MR procedures that out-of-date indications and dosage regimens are seen in the SPCs of generic products. This causes risks for evidence-based and prudent use of antimicrobial products. The situation is also very confusing for the practitioners. **Proposed change:** None.	Comment acknowledged.
Lines 393-394	1	**Comment:** *FVE welcomes the CVMP intention to present a reflection paper on the importance of "off-label" use of antimicrobials in animals, as Cascade is vital for ensuring the health and welfare of certain species (especially for MUMS).* **Proposed change:**	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 393-401	2	**Comment:** We fail to see any greater risks on antimicrobial use under cascade than when used in the accordance with the SPC if the use in both cases in based on best scientific knowledge and prudent use principles are being followed. On a small market there are not enough products thus cascade is only way to use antimicrobials for the treatment. **Proposed change:** None.	Partly agreed; however, “off-label” use is not always supported by a good evidence base or considerations of AMR risks. CVMP agrees with the need for the Cascade.
Lines 403-405	2	**Comment:** The aim to guide industry on the appropriate pack-sizes is welcomed. Many packs contain multiple times more tablets or intramammaries needed for the treatment. The pharmacies are unwilling to divide the packages. **Proposed change:** None.	Comment acknowledged.
Lines 403-405	6	**Comment:** This is normally already taken into account by the companies. However, definition of an appropriate pack size might be challenging in case a product is approved for multiple animal species, where weight differences can be important e.g. a piglet compared to an adult steer etc.	Agreed. Guidance has been prepared, see answer to question 2 of the Question and answer on the CVMP guideline on the SPC for antimicrobial products (EMA/CVMP/414812/2011-Rev.2).
Lines 403-405	7	**Comment:** The PGEU supports the proposal to provide guidance for industry on the appropriate pack-sizes for antimicrobial veterinary medicinal products.	Comment acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change:	
Lines 406-407	1	**Comment:** *FVE strongly supports it.* **Proposed change:**	Noted.
Line 412	5	**Comment:**More than consider **Proposed change:** "The CVMP will ensure that advice provided in SPCs facilitates the development of such guidelines". [i.e. delete "aim to"]	Accepted.
Line 425	5	**Comment:**EAHP welcome the reference to quality assuring veterinary medicinal products. However, knowing the problem of AMR has linkage to quality of medication, it is disappointing that greater reference to this issue does not appear in the paper. We would like to see the final version of the strategy give more consideration to this aspect. This matters not only in respect to production of VMP, but also in respect to management issues, such as how VMP are stored and managed up to the point of application to the animal.	Under Aim 5, reference has now been made to the EC's Prudent Use Guidelines which provide some advice to all responsible parties in this respect.
Line 428	1	**Comment:** *FVE particularly welcomes acknowledgement of FVE in the CVMP Strategy paper and reaffirm our commitment to work in close collaboration with the Agency and CVMP.*	This is appreciated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change:	
Lines 434-438	9	**Comment:** specific actions, in particular in the field of international cooperation, should be described	This is a high level strategy, not suitable for defining specific actions.
Line 437	1	**Comment:** **Proposed change:** We will ***increase collaboration*** ~~***collaborate***~~ with colleagues	Partly accepted.