

19 July 2018 EMA/CVMP/AWP/598285/2015 Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on draft '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)

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

Stakeholder no.	Name of organisation or individual
1	Jodi Lindsay, St George's, University of London, UK
2	Federation of Veterinarians of Europe (FVE)
3	Association of Veterinary Consultants
4	Alliance to Save Our Antibiotics
5	Animalhealth Europe (formerly known as IFAH-Europe)

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## 1. General comments – overview

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2	FVE is strongly committed to fighting antimicrobial resistance and ensuring the public health as well as animal health and welfare. However veterinary profession questions whether the extra administrative burden will outweigh the added value of this guideline as part of the Marketing Authorisation applications for new antimicrobial substances. We are concerned that the additional requirements for any potential applicant may be a disincentive to any company and hamper innovation of new antibiotics for use in animals.	AMR is an important public health issue and should be addressed in line with current regulatory requirements under Directive 2001/82/EC and in future under the new Veterinary Medicines Regulation. The aim of the guideline is to provide a more structured and transparent approach, and hence to improve regulatory predictability for industry with the aim of encouraging development of new antimicrobial substances. The views of industry will be taken into account in the revisions.
	<ul> <li>Reading through the document, some additional questions come up, namely: <ul> <li>It is not clear whether the guidance is meant to be applied to applications of any new product of an existing class of antimicrobial, e.g. the fluoroquinolones, and/or new chemical entities.</li> <li>A separate risk assessment should be provided also for the production type or animal category, in addition to each formulation/ animal species/ indication/ dosing regimen.</li> <li>This guideline exempts any generic application which is hard to justify, especially since there is evidence that when generics – especially generics of generics - are licensed, resistance pressure grows enormously.</li> <li>'Release assessment' should be better explained, introducing also some examples in order to be clear to the applicants.</li> </ul> </li> </ul>	Section 4 outlines when the guidance applies. The Release assessment allows for the production type to be taken into account to refine the assessment. Generic applications under Article 13.1 are exempt from the need to provide safety data except for an ERA. If an AMR risk is identified, then all related products could be addressed under a referral procedure for the class. Some examples on interpretation of data are given.

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	<ul> <li>PK/PD of the antimicrobial: Antimicrobial medicines classified according to type of killing action are as follows: Concentration-dependent killing, time-dependent killing and co-dependent killing. The last is missing.</li> <li>It is not clear in the document if the term food-producing animals refers any food-producing species, including aquatic ones.</li> </ul>	Added. Addressed as required. Fish are included as a food- producing species under EU legislation and it is not usual to clarify this when the term is used.
	We acknowledge the existing risk to public health from antimicrobial resistance due to the use of an antimicrobial in food-producing animals and agree that monitoring of development of resistance of any substance is crucial and should be ongoing. However FVE feels that development of new antimicrobial substances for use in animals should be encouraged and any measures to be taken should be proportionate and ensure that innovation in veterinary science continues.	Agreed.
3	The Association of Veterinary Consultants is grateful to have the opportunity to comment on this proposed new guideline. Antimicrobial resistance (AMR) is a very topical subject but it is of interest that the contribution of AMR caused by antimicrobial use in animals to man, in comparison to AMR produced in man by human use of antimicrobials has not been thoroughly investigated before. As more and more data is being developed, it is becoming quite clear that most of human AMR issues are caused by man's/medical (mis)use of antimicrobials directly in man. With improved genetic characterisation of resistance genes, although they may be the same type of gene, they have generally been found to be very different between animals and man when using advanced techniques such as multi-locus sequence typing (MLST) (Wu et al, 2013). Contamination	It is recognised that some good quality microbiological risk assessments have been published. As more data become available in future, a quantitative approach will be more feasible. At this time the purpose of the risk assessment is to assess the risk qualitatively and to identify broadly high risk scenarios so that risk management measures can be applied.

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	of the environment by human sewage is also a major potential	
	contributor to human resistance development (SVARM, 2015), let	
	alone visits to hospital, where methicillin-resistant Staphylococcus	
	aureus (MRSA), extended-spectrum beta lactamase (ESBL)	
	resistance and carbapenemase resistance are all of major concern.	
	The assessment of risk to public health has always been a part of the	
	Expert Assessment of dossiers relating to antimicrobials for use in	
	animals and generally has played a role in the Benefit/Risk	
	Assessment of an antimicrobial product. Assessing the risk of	
	transmission from animals to man of zoonotic bacteria such as	
	Salmonella and Campylobacter spp has been the major concern and	
	to some extent these can be quantified. The attribution from	
	individual animal species is not always clear but recent work, again	
	apportioning strains from animal species causing disease in man by	
	advanced genetic means, has been extremely useful in determining	
	the attribution to each animal species and even the environment.	
	This is the case with Campylobacter spp particularly (Mughini Gras et	
	al, 2012). Salmonella spp were also relatively easy to apportion to	
	animal species, with S. enterica Enteritidis primarily associated with	
	chickens and eggs but it is much harder now and more effort should	
	be made to apportion S. Typhimurium. As S. Enteritidis cases have	
	fallen so rapidly in the EU (over 50%), S. Typhimurium is becoming	
	numerically more important. The commensal indicator bacteria such	
	as Escherichia coli and Enterococci spp are also of additional benefit	
	to examine but their attribution to resistance development is much	
	harder in many ways as they do not cause disease. SVARM (2015)	
	showed ESBL resistance transfer in E. coli to be minimal (1/379 blood	
	infections in man).	
	The finding of widespread MRSA infections in pigs and the extensive	
	spread of ESBLs in poultry E. coli, associated with the use of third	

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	generation cephalosporins was very disappointing. However, as examples of what can go wrong, could it have been predicted or anticipated before registration that their widespread use would occur and the resulting effect would have developed, especially for an injectable therapeutic antibiotic, and one that was not specifically indicated for use in chickens. EMA did respond very quickly when the problem was identified and this contraindication has made a major impact on subsequent reported ESBL incidence. As more attribution data becomes available a more quantifiable risk assessment will become available. At the moment it is meant to be a qualitative assessment but in the Guidelines these have not been classified sufficiently. If a quantifiable risk assessment is made the risk has not been established either. Is it one, 10 or 100 cases/100,000 population, what will be the breakpoint before action will be required? Are you requiring the transmission rate of the bug and the resistance, does it have to cause treatment failure or even death? What are the likely cut-off points? It may be that that this assessment work is at an early stage and this will evolve and flexibility is more beneficial, currently. Direct transmission of resistance or infections to man/workers from animals is a new part of the Benefit/Risk Assessment. Consistently, when MRSA CC 398 was found in man 90% of cases were people who worked with pigs (Danmap, 2011). Eighty three percent of German pig farmers/stockmen were found to be carrying the organism (Cuny et al, 2009) but not necessarily the organism was causing any clinical disease. Working closely with animals frequently leads to the sharing of bacteria; it is the nature of the work. Twenty one percent of UK pig workers were seropositive to Streptococcus suis (Barlow et al, 2003), approximately 20-30% of pig farms are affected with the disease. In contrast Nijsten et al (1996) in the Netherlands found that the	The guidance proposes that the consequences for vulnerable sub-populations should be considered and it is probable that risk management measures (although not addressed in the guideline) would be tailored to the identified risk, if possible.

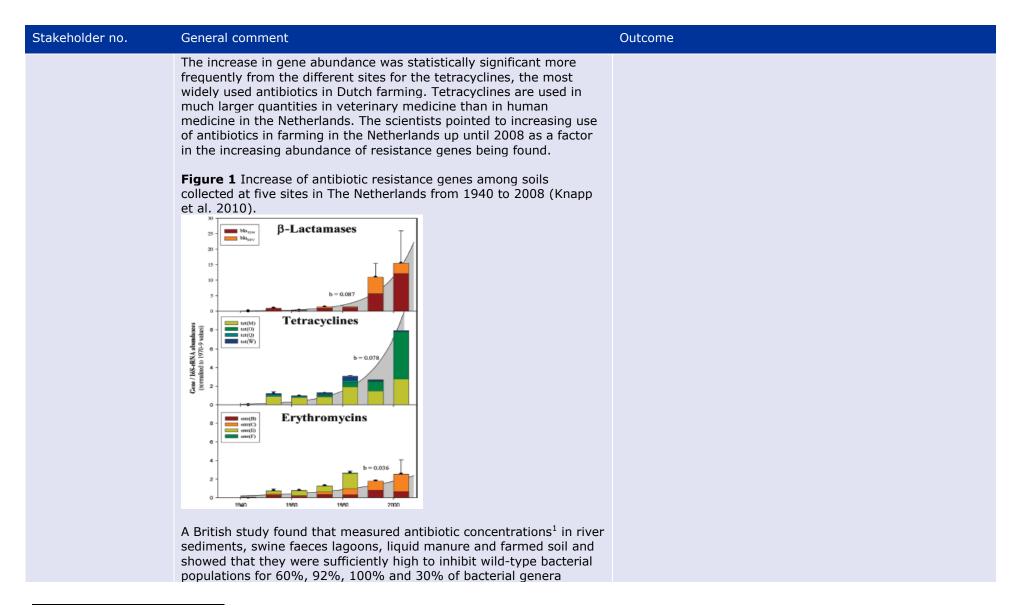
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	<ul> <li>antibiotic resistance of E. coli in faecal samples of pig farmers was significantly lower than samples obtained from pigs. The resistance patterns of only 4% of farmer E. coli were the same as pigs from the same farm. Will this risk assessment be based on direct contact personnel in which case any resistance transmission will be relatively high to workers, or will it be correlated with the number of workers and the human population in general? If an antibiotic causes resistance will there be a warning statement that this may cause resistance in workers in close contact with the animals or will further steps be taken?</li> <li>Should it apply to generic antimicrobials, especially if there are future product referrals or reviews of older products, which has been proposed?</li> <li>There is concern that it is not sure where this part of the resistance assessment will finally lead. It is felt that possibly this direct assessment and the indirect human transmission risk assessment should be discussed in more detail in an open forum to ascertain more clearly the objectives and endpoints.</li> <li>References:</li> <li>Barlow, A.M., Hunt, B.W., Heath, P.J. and Smith, R.M.M. (2003) The prevalence and clinical diseases caused in pigs by different serotypes of Streptococcus suis (June 200-September 2002) and human infection (1981 to October 2002) in England and Wales. Pig Journal, 51, 164-176.</li> <li>Cuny, C., Nathaus, R., Strommenger, B., Altmann, D. and Witte, W. (2009) Nasal colonization of humans with methicillin-resistant Staphylococcus aureus (MRSA) CC398 with and without exposure to pigs. PLoS ONE, August: pp e6800.</li> </ul>	Generic applications under Article 13.1 are exempt from the need to provide safety data except for an ERA. If an AMR risk is identified, then all related products could be addressed under a referral procedure for the class.

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	Danmap 2010, (2011) Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark.	
	Mughini Gras, L., Smid, J.H., Wagenaar, J.A. et al (2012) Risk factors for campylobacteriosis of chicken, ruminant and environmental origin: a combined case-control and source attribution analysis. PLOS One, 7 (8), e42599.	
	Nijsten, R., London, N., van den Bogaard, A. and Stobberingh, E. (1996) Antibiotic resistance among Escherichia coli, isolated from faecal samples of pig farmers and pigs. Journal of Antimicrobial Chemotherapy, 37, 1131-1140.	
	SVARM, 2014 (2015) Consumption of antibiotics and occurrence of antibiotic resistance in Sweden, p 48.	
	Wu, G.H., Day, M.J., Mafura, M.T., Nunez-Garcia, J., Fenner, J.J., Sharma, M., van Essen-Zandbergen, A., Rodriguez, I., Dierikx, C., Kadlec, K., Schink, A-K., Wain, J., Helmuth, R., Guerra, B., Schwarz, S., Threlfall, J., Woodward, M.J., Woodford, N., Coldham, N. and Mevius, D. (2013) Comparative analysis of ESBL-positive Escherichia coli isolates from animals and humans from the UK, the Netherlands and Germany. PLOS ONE, Vol, 8, Issue 9, e75392.	
4	The Alliance to Save Our Antibiotics (ASOA) welcomes the CVMP's aim of providing a systematic of scientific data on the risks to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals.	
	While we welcome many aspects of the document, in this consultation response we will focus on three key areas where we believe this guidance document should be improved:	The CVMP acknowledges the importance of the issue of AMR in the environment and is currently considering the matter in the context of VMP use in a separate reflection paper.

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	be done in this area, we believe there is already enough evidence of farming significantly increasing the size of the environmental reservoir of resistant bacteria and resistance genes, and of environmental transmission to humans.	
	Studies have shown that manure from intensively farmed pigs and poultry are reservoirs of antibiotic-resistant bacteria, including potential pathogens such <i>Staphylococcus</i> and <i>Enterococcus</i> , that typical storage practices on poultry farms are insufficient to eliminate these bacteria before the manure is spread on land and that seepage from pig manure lagoons can result in antibiotic resistance genes contaminating groundwater (Wellington et al. 2013, Graham et al. 2009, Koike et al. 2007).	
	Scientists have also shown that urine from cattle treated with the modern cephalosporin ceftiofur contains metabolites which exert significant antibiotic selective pressure on <i>E. coli</i> (Subbiah et al. 2012). They found that the selection of antibiotic-resistant <i>E. coli</i> in soil was "much more dramatic" than the reported selection <i>in vivo</i> following parenteral administration. The scientists said that "the dramatic expansion of ceftiofur-resistant enteric bacteria in food animal populations could be explained in part through a process of environmental selection and transmission back to food animals".	
	American studies have shown that living in proximity to livestock farms or areas where manure is applied may increase the risk of acquiring MRSA colonisation or developing an infection (Casey et al. 2013, Carrel et al. 2014). Similarly, a study found that in the Netherlands people living in livestock-dense areas who do not have direct contact with farm animals are also at increased risk of being carriers of livestock-associated MRSA (Feingold B.J., 2012).	
	A study of antibiotic-resistance gene abundances in archived soils taken from different locations in the Netherlands showed that the quantities of antibiotic-resistance genes increased significantly for all classes of antibiotics studied between 1940 and 2008 (Knapp et al. 2010). See Figure 1.	



<sup>&</sup>lt;sup>1</sup> The antibiotic concentrations were measured in different studies carried out in different parts of the world.

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	respectively (Tello et al. 2012). The scientists said: "The potentially affected fractions for ciprofloxacin, erythromycin, and tetracycline at measured environmental concentrations of river sediments, swine feces lagoon sediments, liquid manure, and farmed soil suggest that these environments are likely to be hot spots for the selection of resistance".	
	The British scientists also showed that environmental concentrations of antibiotics used deemed acceptable in EU risk assessments are in fact sufficiently high to exert a selective pressure on clinically relevant bacteria.	
	They concluded that "to minimize the potential effect of antibiotic pollution on antibiotic resistance, resistance—or a proxy thereof— should be considered in environmental risk assessment of human and veterinary antibiotics".	
	ASOA agrees with the recommendation of these scientists to consider the effects on antibiotic resistance of antibiotic pollution. Existing data gaps should not be used as a reason for ignoring the issue.	
	On lines 48 to 50, the CVMP says when referring to the general antimicrobial-resistance human-health risks of farm antibiotic use that, "It is recognised that there will be data gaps and therefore it is recommended that a qualitative approach is taken to give a final estimation of the overall risk to public health due to AMR". Given this principle, it is unclear why the CVMP are excluding environmental contamination from the overall risk assessment.	
	<b>1.2. Off-label use of antibiotics</b> The off-label use of antibiotics is not included within the risk assessment even though this form of use remains widespread in the EU and has already had a major impact upon human health.	
	As noted by EFSA in a 2011 report on cephalosporin-resistant bacteria from food animals, "due to poor compliance with this regulation [on off-label use] and possibly also differences at the level of national implementation, such use is probably much more	

The L imple Direct of ex preve Veter and t label Veter As no Mem propl eggs chick (Ove huma are b can o Altho coun no lo certa not t antib	Proprehensive than foreseen in legislation" (EFSA 2011). UK is an example of a Member State which has failed to correctly lement the EU Directive governing off-label use. Article 11 of active 2001/82/EC says that off-label use can only occur "by way exception". This means that any routine use, including routine ventative use, is illegal according to EU law. Unfortunately, the UK erinary Medicines Legislation (2013) does not include this phrase therefore routine off-label use, including routine preventative off- el use is, in certain circumstances, permitted off-label (The erinary Medicines Regulations 2013). noted by EFSA, as a result of this regulatory failure, in some mber States modern cephalosporins have been used phylactically in day-old piglets and in day-old chicks, or even s. Off-label use explains why such a high percentage of retail cken meat is now contaminated with ESBL resistant <i>E. coli</i> erdevest et al. 2011, Ghodousi et al. 2015). This is a significant nan-health issue since ESBL <i>E. coli</i> from poultry and chicken meat believed to be a significant reservoir of resistance plasmids which disseminate to humans (de Been et al. 2014). nough, due to voluntary bans and legislative action in some ntries, the extent of off-label use of modern cephalosporins may onger be as great as it was a few years ago, it remains legal in rain Member States like the UK and cannot therefore be assumed to be occurring. Furthermore, routine off-label use of other biotics may also be occurring. mough the EU Directive already excludes routine off-label use, the EFSA's 2011 report highlighting the lack of implementation no ctive action appears to have been taken to ensure that the active is implemented correctly in all Member States. This failure thes after the Directive itself had already been amended to enable re widespread off-label use – the Directive previously only mitted off label use in "an animal or to a small number of animals a particular holding", whereas this restriction has now b	
(Offic	icial Journal of the European Communities, 2001).	

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	This long-standing lax regulatory approach to off-label use will again be reinforced if it is decided by the CVMP to exclude the practice from the antimicrobial-resistance risk assessment.	
	<b>1.3.</b> Selection for antimicrobial resistance at doses below the Minimum Inhibitory Concentration (MIC) The guidance document, like the benefit-risk assessment in general, does not sufficiently take into account the dangers of selection for antibiotic resistance at doses below the MIC.	
	In recent years, it has been established for various antibiotics used in human and veterinary medicine that selection for antibiotic resistance occurs at concentrations which can be a small fraction of the MIC.	
	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 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 (Gullberg et al. 2011). They determined a Minimum Selective Concentration (MSC) above which the antibiotic exerted a selective pressure in favour of resistant bacteria. For the <i>Salmonella</i> stains examined, the MSC of	
	streptomycin and tetracycline were found to be respectively just 1/4 and 1/100 of the corresponding MICs. For <i>E. coli</i> , the MSC of ciprofloxacin was either 1/10 or 1/230 of the MIC, depending on the resistance mutation.	

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	These findings, and similar findings in other work (Gullberg et al. 2014, Liu et al. 2011, Hughes and Andersson 2012) suggest that risk assessments that consider only selection to occur at the MIC or at higher concentrations are failing to recognise the selection that occurs at lower doses. Resistant mutants selected at low antibiotic concentrations are generally more fit than those selected at high concentrations but can still be highly resistant (Sandgren 2014).	
	Sub-MIC selection for antibiotic resistance may occur in the animal, in the environment and in humans consuming food with antibiotic residues. ASOA believes that risk assessments should be required to take fully into account resistance selection at sub-MIC levels.	
	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 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 <i>E. coli</i> is the most sensitive species to enrofloxacin, and a MIC <sub>50</sub> for <i>E. coli</i> is used in setting the Microbiological ADI (CVMP 1998). 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 (CVMP 2002).	
	However, the principal metabolite of enrofloxacin is the human antibiotic ciprofloxacin and, as mentioned above, the <i>E. coli</i> 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	

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	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.	
	Similarly, selection for resistant bacteria in the animal's gastrointestinal tract will occur at much lower concentrations than is assumed by taking an MIC approach.	
	References	
	Knapp et al. 2011, Antibiotic Resistance Gene Abundances Correlate with Metal and Geochemical Conditions in Archived Scottish Soils, <i>PLoS One</i> , 6	
	Knapp et al. 2010, Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940, <i>Environmental Science and Technology</i> , 44	
	Wellington et al. 2013, The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria, <i>Lancet Infectious Diseases</i> , 13	
	Graham et al. 2009, Fate of antimicrobial-resistant enterococci and staphylococci and resistance determinants in stored poultry litter, <i>Environmental Research</i> , 109	
	Koike et al. 2007, Monitoring and source tracking of tetracycline resistance genes in lagoons and groundwater adjacent to swine production facilities over a 3-year period, <i>Applied and Environmental Microbiology</i> , 73	
	Subbiah et al. 2012, Urine from Treated Cattle Drives Selection for Cephalosporin Resistant Escherichia coli in Soil, <i>Plos One</i> , 7	

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	Casey et al. 2013, High-density livestock operations, crop field application of manure, and risk of community-associated methicillin- resistant Staphylococcus aureus infection in Pennsylvania, <i>JAMA</i> <i>Internal Medicine</i> , 173	
	Carrel et al. 2014, Residential proximity to large numbers of swine in feeding operations is associated with increased risk of methicillin- resistant Staphylococcus aureus colonization at time of hospital admission in rural Iowa veterans, <i>Infection Control and Hospital Epidemiology</i> , 35	
	Feingold B.J., 2012. Livestock density as risk factor for livestock- associated methicillin-resistant Staphylococcus aureus, the Netherlands, <i>Emerging Infections Diseases</i> , 18	
	Tello et al. 2012, Selective Pressure of Antibiotic Pollution on Bacteria of Importance to Public Health, <i>Environmental Health Perspectives</i> , 120	
	EFSA 2011, Scientific Opinion on the public health risks of bacterial strains producing extended-spectrum $\beta$ -lactamases and/or AmpC $\beta$ -lactamases in food and food-producing animals	
	The Veterinary Medicines Regulations 2013, Schedule 4, Administration under the cascade	
	Overdevest et al. 2011, Extended-spectrum $\beta$ -lactamase genes of Escherichia coli in chicken meat and humans, The Netherlands, <i>Emerging Infectious Diseases</i> , 17	
	Ghodousi et al. 2015, Extended-Spectrum ß-Lactamase, AmpC- Producing, and Fluoroquinolone-Resistant Escherichia coli in Retail Broiler Chicken Meat, Italy, <i>Foodborne Pathogens and Disease</i> , 12	
	de Been et al. 2014, Dissemination of Cephalosporin Resistance	

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	Genes between Escherichia coli Strains from Farm Animals and Humans by Specific Plasmid Lineages, <i>Plos One</i> , 10	
	Official Journal of the European Communities, 2001 http://ec.europa.eu/health/files/eudralex/vol- 5/dir 2001 82/dir 2001 82 en.pdf	
	Gullberg et al. 2011, Selection of Resistant Bacteria at Very Low Antibiotic Concentrations, <i>Plos Pathogens</i> , 7	
	Gullberg et al. 2014, Selection of a Multidrug Resistance Plasmid by Sublethal Levels of Antibiotics and Heavy Metals, <i>MBio</i> , 5	
	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, <i>Antimicrobial Agents</i> <i>and Chemotherapy</i> , 55	
	Hughes and Andersson 2012, Selection of resistance at lethal and non-lethal antibiotic concentrations, <i>Current Opinion in Microbiology</i> , 15	
	Sandgren 2014, Selection of antibiotic resistance at very low antibiotic concentrations, <i>Uppsala Journal of Medical Sciences</i> , 119	
	CVMP 1998, Enrofloxacin, Summary report (2) CVMP 2002, Enrofloxacin, Summary report (5)	
5	IFAH-Europe welcomes the opportunity to comment on this draft guideline, it provides clarity on the types of information needed for an analysis of risk to public health from antimicrobial resistant bacteria resulting from the intended use of the proposed veterinary medicinal product.	

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	However, it is lacking in guidance or a framework on how the different pieces of information will or should be categorized/ranked with respect to risk outputs (Low, Medium or High) for the release, exposure and consequence assessments, and how these outputs are integrated to an overall assessment for purposes of the authorization process and considerations of label restrictions. More specifically, since there are no definitions of Low, Medium or High risk, the assessment can be construed as being very open-ended and there is no transparent way for a Sponsor to make any preliminary assessment if the level of risk will be acceptable. While we acknowledge that a lack of definitions for Low, Medium or High risk permits flexibility, the lack of a framework leaves much uncertainty in the approval process. We would therefore welcome a similar approach as the framework provided in FDA Guidance 152.	To be addressed at Focus Group Meeting. We have introduced some further guidance on categorisation of the risk factors. These can be further refined by the applicant according to the proposed conditions of use of their product. Categorisations/scales are also given for the release, exposure and consequence steps. For the overall risk estimation, a matrix could be seen as somewhat arbitrary and without this the risk assessors would have greater flexibility to use their expert judgement.
	The lack of predictability and transparency in this new requirement could have the unintended consequence of further discouraging investments in e.g. optimising dosing regimens that would contribute to responsible use of an existing product. In contrast, there is no risk assessment requirement for any new generic authorization. Consequently, the guideline provides an incentive for companies to focus on increasing the numbers of generic drug applications. This is even more plausible as newer and sometimes critically important antibiotics are out of patent protection or coming closer to the end of patent life. Generics are one of the major contributing factors in changing use patterns of veterinary medicinal products and therefore cannot be excluded from this guideline.	Generic applications under Article 13.1 are exempt from the need to provide safety data except for an ERA. If an AMR risk is identified, then all related products could be addressed under a referral procedure for the class.

Stakeholder no.	General comment	Outcome
5	Two risk assessments are requested: risk of resistant bacteria that may be transmitted (1) through food products of animal origin, and (2) risk of bacteria that may be transmitted by direct contract through the target species. Are these to be addressed separately or as a composite risk? None of the methodologies for risk assessment cited in footnotes 5-8 (Section 5) address the risk via <u>direct contact</u> , and so this is a new risk assessment as compared to other guidance cited by the Agency. Thus the proposed guidance includes a new, unprecedented requirement unlike any requested worldwide, with no framework reference on how the assessment is to be completed, nor how it is used in comparison with the food-borne route of analysis.	To be addressed at Focus Group Meeting Although it is acknowledged that there are even more data gaps in regards to transmission of AMR via the direct contact route, this aspect is a relevant concern that is being increasingly recognised (Marshall & Levy, 2011) <sup>2</sup> . The basic framework for the risk assessment is the same for both contact and foodborne routes. As an example, Alban et al (2012) used the framework to estimate the human health risk due to MRSA CC398 as a result of pleuromutilin use in pigs. Some examples are given in the guideline of data that could be presented. It is envisaged that a separate risk estimation would be provided for each hazard identified,
	Regulatory requirements should be transparent, with a modicum of predictable outcome, and where possible, harmonized with other developed countries: in this case, the risk assessment of public health impact by direct contact is inconsistent with the CODEX guidelines, as well as other agencies, as the guidelines cited in this document evaluate risk by foodborne routes, not by direct contact. Presuming that the organism of concern is Methicillin Resistant <i>Staphylococcus aureus</i> (MRSA), we would like to point out that a risk assessment has jointly been published by ECDC, EFSA and EMA: http://www.ema.europa.eu/docs/en_GB/document_library/Report/20	although there will be much data in common. For hazards that are potentially transmitted through both direct contact and the foodborne routes, as the exposure pathway will differ, the final risk estimation may differ for the two routes. Separate assessments potentially will allow tailoring of risk management measures. Although ECDC/EFSA/EMA provided a risk assessment for MRSA in 2009, the situation is evolving and other hazards of importance may also be identified moving forwards.

<sup>&</sup>lt;sup>2</sup> Marshall B, Levy SB. Food Animals and Antimicrobials: Impact on Human Health. Clinical Microbiology Reviews, 2011, pp.718-733.

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Stakeholder no.	General comment	Outcome
	<u>09/10/WC500004306.pdf</u> . From this risk assessment it is clear that	
	LA-MRSA (CC398) represents only a small proportion of the total	
	number of reports of human MRSA infections in Europe and that	
	CC398 is only rarely associated with deep-seated infections of skin	
	and soft tissue, pneumonia and septicaemia in humans. We question	
	whether a systematic risk assessment before marketing authorization	
	is the most appropriate way to mitigate risk in this particular case.	
	Numerous management options are summarized in the ECDC, EFSA,	
	and EMA joint assessment: biosecurity, reduction of antimicrobial	
	selection pressure in general (note that this is not as easy as	
	restricting the use of one particular molecule/class!), hygiene	
	measures, surveillance etc. We therefore believe that the risk	
	assessment related to bacteria that may be transmitted by direct	
	contact with the target animal species should be removed from this	
	draft guideline and that the risk assessment should be limited to	
	resistant bacteria that may be transmitted through the foodborne	
	route. Should EMA CVMP maintain the opinion that the direct contact	
	route needs to be taken into account, an additional algorithm on how	
	to interpret the available data to form a risk assessment as well as	
	clarity around the scope (MRSA only or applicable to other organisms	
	as well?) is needed. The draft guideline is currently identifying	
	hazards, but it does not explain how how the different pieces of	
	information will be applied or categorized/ranked with respect to risk	
	outputs (Low, Medium or High) for the release, exposure and	
	consequence assessments, and how these outputs are integrated to	
	an overall assessment. It needs to be understood that such	
	framework for the direct contact route is currently not available from	
	FDA Guidance 152 or other guidance worldwide, since those are	
	limited to the foodborne route of transmission.	

Stakeholder no.	General comment	Outcome
	To summarise, we have major concerns around two important differences between the currently proposed CVMP Guideline and FDA Guidance 152 and other guidance worldwide:	
	<ul> <li>CVMP does not only request a risk assessment for exposure through the foodborne route, but additionally introduces the 'direct contact with treated animals' route. We urge for the latter component to be removed from the CVMP risk assessment Guideline as currently drafted.</li> </ul>	
	There are no definitions for Low, Medium or High risk, nor is there an integration framework provided, which makes the whole process arbitrary and unpredictable. We request for the same definitions and framework as in FDA Guidance 152 to be incorporated in the CVMP Guideline.	
5	We would like to point out that, for a diverse landscape of EU countries differing in use patterns of antimicrobials, husbandry systems, consumption patterns of meat, milk and offal among others it is extremely challenging to generate data depicting the chain of events which needs to be followed up throughout the whole food chain.	Unless the intention is for an EU-wide MA, then the data provided should be relevant for the region where the application is made. For an EU-wide application, then overall EU data should be provided but with any exceptional regional differences brought to attention. This issue is now addressed in section 5.
	This scenario includes several assumptions which cannot be depicted easily in numbers. In view of uncertainties about the availability and relevance of published data or references, exposure and consequence assessment would be based so far on many assumptions and estimates. Also, there are currently virtually no official proposals for comparative rankings for details like consumption, attribution, exposure, prevalence, transmission etc. as a basis for objective	Guidance has now been included on data/rankings for certain risk factors that are not product dependent (e.g. food consumption patterns). These may be refined by the applicant where further supporting data are available and to take account of the conditions of use of the individual product. Acknowledging the data gaps, an optional pragmatic approach to the consequence assessment is also provided.

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Stakeholder no.	General comment	Outcome
	comparable assessments for regulatory decisions.	
	Furthermore secondary contaminations of animal products are by far more likely to cause human illness. But those are hard to differentiate from the above mentioned scenario and could be due to humans contaminating the product as well.	The guidance has been amended to advise that applicants can submit data on secondary contamination, which should be excluded from the risk estimation.

## 2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(To be completed by the Agency)
301	1	Comments: Co-selection does not only occur because multiple resistances are part of the same operon. Proposed change: 'This can occur because the multiple resistance genessame promotor.' And add: ' It can also occur because multi-drug resistant clones are selected by the use of any of the antimicrobials they are resistant to.'	Partly accepted. The definition has been amended to reflect that agreed in other documents recently published by CVMP.
Several sections of the text	4	Comment: See section 1.1. of General comments above Proposed change (if any): Several sections of the text should be amended so that: - environmental contamination by resistant bacteria, antibiotics and metabolites is recognised as a likely contributor to antibiotic resistance in human pathogens - environmental contamination is considered within the risk assessment.	Not accepted. See response in General comments section.
Lines 93-94	4	Comment: See section 1.2. of General comments above Proposed change (if any): "Off label" use must be considered within the risk assessment.	Not accepted. See response in General comments section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(To be completed by the Agency)
Line 207	4	Comment: See section 1.3 of General comments above Proposed change (if any): Add "The dossier must include data on the Minimum Selective Concentration (MSC) for different bacteria. "	See response in General comments section. An amendment is not relevant for this section of the guideline, but see below.
Table 1, column 1, row 5	4	Comment: See section 1.3 of General comments above Proposed change (if any): Susceptibility data (MIC distribution /MBC, Minimum Selective Concentration) for the bacteria of human health concern.	It is considered more relevant to address the MSC in the release assessment and a revision has been included to refer to the MSC in Table 2.
Table 1, column 2, row 5	4	Comment: See section 1.3 of General comments above Proposed change (if any): Add "Minimum Selective Concentrations should also be determined."	See above.
76	5	Comments: Contrary to line 69 this bullet reads as if the Guideline extends to all "Veterinary Medicinal Products (VMPs)" not just "antimicrobial VMPs. Proposed change: <u>Antimicrobial</u> Veterinary Medicinal Products (VMPs) intended to treat food producing species, and	Accepted.
106-108 in relation with 119	5	<b>Comments</b> : This draft guideline precisely describes the cases supposed to increase the use of antibiotics, and therefore the risk of AMR. Regardless of the	Not accepted. Generic applications under Article 13.1 are exempt from the need to provide safety data except for an ERA. If an AMR risk is identified, then all related products

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		current EU regulatory/legal pressure for decreased antibiotic use, we consider that a generic product also has the potential to increase the use of antibiotics, because of the downward pressure exerted on price. Thus for completeness this draft guideline should also apply to generic antibiotic products. <b>Proposed change</b> : Include generic products in the VMP requiring a risk assessment and delete the sentence in 119 'The guidance does not apply for generic applications made under Article 13.2 of the Directive.'	could be addressed under a referral procedure for the class.
140	5	Comment: Footnote number 8. Hyperlink is out of date. Proposed change: <u>http://apvma.gov.au/node/1018</u> or <u>http://apvma.gov.au/registrations-and-</u> <u>permits/data-guidelines?qt-data_guideline_tabs=1#qt-</u> <u>data_guideline_tabs</u> and look for Part 10.	The hyperlink has been corrected.
152-155	5	<b>Comment:</b> This section seems to be contradictory to the statement in lines 139-140. Starting from the point of release (slaughter), where handling and processing methods really determine exposure?	Not fully understood. The exposure still needs to be addressed in the assessment, although less emphasis is placed on this part.
222 Table 1, last row	5	<b>Comment:</b> This row refers to bacteria of human health concern. Clinical breakpoints for bacteria of human health concern may not exist for compounds	Accepted. Amendment made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
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		which are not licensed for use in human medicine. Additionally "Clinical and microbiological breakpoints (ECOFFs)" should be amended to "Clinical breakpoints and epidemiological cut-off values (ECOFFs)", because the designation "breakpoint" is limited to the clinical context (Clinical breakpoint is the numerical value used to indicate whether a clinical pathogen is susceptible or resistant to an antimicrobial). In this respect, it is desirable to add a definition of clinical resistance to the Definitions on page 17 and 18, for instance, the terminology applied by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (see comments to lines 278-323). <b>Proposed change:</b> Clinical breakpoints or microbiological breakpoints epidemiological cut-off values (ECOFFs) should be considered in the assessment, where possible.	
224	5	<ul> <li>Comment: This sentence is unclear for clarity we would suggest amending. The bacteria can cause human illness and that depends on their pathogenicity/virulence, not the resistance determinants?</li> <li>Proposed change: development of antimicrobial-resistant bacteria /determinants that could result in resistant infections in humans, and</li> </ul>	Accepted. Amendment made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome (To be completed by the Agency)
231	5	<b>General comment:</b> The 'conditions of use' the 'production type and the husbandry practices' should be taken into account. Those could differ to a great extent for example within one country but also from country to country (extensive or intensive husbandry). Therefore for the individual animal and the respective person in contact or at risk there might be huge differences. <b>Proposed change:</b> Amend to incorporate similar wording to FDA guidance 152: Information regarding proposed conditions of use including route of administration, dosing regimen, proposed product indication, intended target animal species, proposed withdrawal time.	This section has been amended. The intention is to give the applicant guidance on additional information that might help to refine the risk assessment, e.g. relating to the prevalence of the proposed indication. If there is variability between e.g. countries, this should also be mentioned as indicated in section 5.
249	5	<b>Comment:</b> In the Table 3 row "a) Human consumption patterns for food produce from target species", the EFSA EU comprehensive Food Consumption Database/Eurostat is provided as reference. However, in this database, global "meat and meat products (including edible offal)" consumption is provided. The detail of this average consumption per species is not available. In addition, there is no information about this food ("crude" or manufactured - such as can, with sterilisation processes during manufacturing - the latter strongly decreased the risk of AMR transmission.). Thus, the use of such database, may artificially overestimate the exposure to AMR of the human population, for VMP intended to be use in either	High level rankings have now been proposed based on EU- wide data; however these may be refined by the applicant e.g. according to species production type, or countries where the MA is sought. This is explained in section 5.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
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		one or two food producing animals species (e.g. cattle or swine or poultry). Then, in case of one antimicrobial VMP intended to be registered and used in specific countries (national registration, MRP or DCP), which rules should the Applicant follow? Lastly, amongst EU countries, the consumption (meat & offal) varies from one country to another. Which reference value should be therefore retained?	
249	5	<ul> <li>Comment: Table 3: exposure assessment row 'b-e'.</li> <li>Who defines relevant bacteria?</li> <li>How to distinguish between secondary contamination with resistant bacteria by the environment or by the handler himself?</li> <li>Proposed change: Amend the text in line with FDA guidance 152</li> </ul>	This step addresses biological pathways necessary for exposure of humans to the hazard(s) (resistant bacteria/determinants); therefore the bacteria are those related to the identified hazard. Examples are now given in Annex 1. The GL has been updated to indicate that the applicant may provide data on secondary contamination, which should be excluded for the purpose of the risk estimation.
263	5	<b>Comment:</b> Table 4: Consequence assessment We propose to evaluate those criteria before the submission of this guideline for some of the antimicrobials. Especially the feasibility to obtain the data for the part 'Number/proportion of cases attributed to animal food produce/animal contact' and 'Prevalence of antimicrobial resistance in human isolates and attribution to animal source (where possible)' is strongly questioned. The provided links are only referring to data on antimicrobial resistance in general in humans, but "lack the data on the occurrence of resistance in isolates from food of animal	We acknowledge the extent of the gaps in the data needed to perform the consequence assessment; nevertheless we find that this is an important part of the risk estimation. An optional simplified pragmatic consequence assessment is proposed based on the AMEG categorisation and extent of use of the AM class in human medicine. This is to be discussed at the focus group meeting.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
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		origin" and "To date, the precise attribution of the different transmission routes of the various foodborne pathogens to the total burden of disease in humans is not known because of shortage in data". (Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report). Only if those data are available and attributing to a proportion of reported antimicrobial resistance in humans this guidance will make a contribution to diminishing resistant bacteria in man. A consequence assessment to the level of details listed is only possible where the necessary data are available for the concerned antimicrobial. As the JIACRA report states: "In this report, the impact of food-borne antimicrobial resistance could therefore not be specified and quantified. Instead, we provided a comparison of data on antimicrobial resistance in food-producing animals and in humans." If the required data are not available and cannot be distinguished from other causes of antimicrobial resistance development we propose to keep only the first two sections on the 'Hazard identification and Release assessment' as depicted already by the VICH GL27 and the 'GL on efficacy studies for antimicrobials'.	
268-277	5	<b>Comment:</b> There is no framework provided, or suggestion of the process of risk estimation integration of release, exposure and consequence assessment of "antimicrobial-resistant bacteria". The terms High,	See General comments above. For discussion at focus group meeting.

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		Medium and Low are considered subjective in this document and the guidance suggest that these terms should be explained where used. <b>Proposed change:</b> Provide a basis/framework for how the data will be integrated for decision making purposes or risk mitigation decisions (e.g. any label restrictions). The terms High, Medium and Low should have some definition in the Guideline, as the current draft already acknowledges that qualitative data analysis will be necessary. Without these outlines, the basis for evaluation from one drug application to the next could be arbitrary.	
278-323	5	<ul> <li>Comment: It is desirable to add a definition of clinical resistance to the Definitions on page 17 and 18, for instance, the terminology applied by the European Committee on Antimicrobial Susceptibility Testing (EUCAST):</li> <li>Proposed change: Please add:</li> </ul>	Clinical resistance is not a term used in the guideline. A reference is made to EUCAST for the definition of 'clinical breakpoint'.
		<ul><li>Clinically Resistant (R)</li><li>A micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.</li><li>A micro-organism is categorized as resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system.</li></ul>	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(To be completed by the Agency)
290-291	5	Comment: Microbiological resistance is defined as is considered to be present if the Minimum Inhibitory Concentration (MIC) exceeds the epidemiological cut- off value". It should be noted that isolates with MICs exceeding the epidemiological cut-off values comprise both decreased susceptible (yet clinically responsive) and clinically resistant isolates. The combination of these two categories has caused much confusion. For some antibiotic classes it is crucial to differentiate between the population characterized by decreased susceptibility and the clinically resistant population. Hence, the definition for "clinical resistance" should be added to the definitions. Moreover, to avoid any misunderstandings, our proposal is to follow the terminology of EUCAST by replacing "microbial resistance" by "non-wild type" or "non-susceptibility": <b>Proposed change:</b> Replace line 290-291: "Microbiological resistance against an antimicrobial is considered to be present if the Minimum Inhibitory Concentration (MIC) exceeds the epidemiological cut-off value." With the following: Wild type (WT) A micro-organism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in	Definitions have been amended for consistency with other documents published by CVMP, as relevant.

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			(To be completed by the Agency)
		question.A micro-organism is categorized as wild type(WT) for a species by applying the appropriatecut-off value in a defined phenotypic test system.Non-Wild Type (NWT)A micro-organism is defined as non-wild type(NWT) for a species by the presence of anacquired or mutational resistance mechanism tothe drug in question.A micro-organism is categorized as non-wild type(NWT) for a species by applying the appropriatecut-off value in a defined phenotypic test system.	
292	5	<b>Comment:</b> The definition of commensal is too broad for purposes of this risk assessment: <b>Proposed change:</b> Suggest specific bacterial species be named, that are intended for analysis, and included in monitoring programs in the EU, such as <i>Enterococcus</i> species and <i>Escherichia coli</i> . It would be impossible to evaluate all commensal organisms as currently defined. While we do not believe a risk assessment of all commensal organisms is intended in this guidance, the current definition creates ambiguity.	The definition has been deleted. Examples of commensal/indicator organisms are now given in Annex 1. The definition of foodborne commensal as provided in VICH GL 27 is included.
296	5	<b>Comment:</b> The definition of co-resistance is too restrictive and should be confined the to the Codex definition. Co-resistance can occur in an organism	The definitions have been revised for consistency with other recent CVMP publications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(To be completed by the Agency)
		wherein more than one resistance genes are present, but not closely linked as described and suggested in lines 299-300: For example a bacterial strain could be resistant to more than one antimicrobial drug class due to a resistance gene "X" found on a plasmid and another, different resistance gene "Y" found on the chromosome. The organism would be co-resistant to antimicrobials targeted by "X" and "Y", could be co- selected by either drug (class), yet resistance to only one drug (class) might be transferred by conjugation even though they are not linked as described in the proposed definition. <b>Proposed change:</b> CODEX [ <i>CAC/GL 77-2011</i> ] defines co-resistance "The ability of a microorganism to multiply or persist in the presence of different classes of antimicrobial agents due to possession of various resistance mechanisms." Delete the EFSA commentary which describes a subset of possibilities within the codex definition.	