EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMA/598105/2014
Veterinary Medicines/CVMP/CHMP

Overview of comments received on 'Answers to the request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals' (EMA/381884/2014)

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

Stakeholder no.	Name of organisation or individual
1	Hans Peder Graversen (Medical Director, Head of Department), AC-fuldmægtig
2	Virbac
3	The British Small Animal Veterinary Association (BSAVA)
4	FVE, Federation of Veterinarians of Europe
5	European College of Porcine Health Management
6	EGGVP – European Group for Generic Veterinary Products
7	British Veterinary Association
8	European Public Health Alliance (EPHA)
9	UK Advisory Committee on the Microbiological Safety of Food
10	Swissmedic
11	IFAH-Europe

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Stakeholder no.	Name of organisation or individual
12	French Authorities
13	Association of Veterinary Consultants

1. General comments – overview

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1	Some of the infection control professionals and clinical microbiologists in Texas now have skimmed through the material and have a relevant alarming concern, as the descriptions contain the following information: The report approved Colistin for veterinary use incl. group medication. There should be objected to a last-resort antibiotic used in veterinary. Although resistance to Colistin is still rare here in Denmark, found it increasingly in human clinical isolates. Since Colistin is one of the last antibiotics we have to treat the highly multidrug-resistant bacteria, it can have serious consequences for the human infection treatment if Colistin resistens selected forward veterinarily.	Due to the last-resort concern, the EU has recently launched an article 35 referral on products containing colistin for oral use in food producing animals. Based on the current evidence, it is considered appropriate to maintain the use of colistin in veterinary medicine given the low level of acquired resistance in target bacteria, but to restrict indications to therapy or metaphylaxis, and to remove all indications for prophylactic use in order to minimise any potential risk associated with a broader use.
2	It is highly appreciated that among factors influencing the possible transfer of antimicrobial resistance to humans from the use of antibiotics in animals, the route of administration is often cited (line numbers 196-407-513 in answer to Question 2 and line numbers 829-977 in answer to Question 3). It highlights that generalisation of antimicrobial categorisation is not possible (line number 198) and that risk management measures should take into account the various factors in the chain of events from the use of antimicrobials in animals to possible antimicrobial resistance issues in humans (line number 404/ figure 1), among which the route of administration in animals.	Noted.
2	In answer to Question 4, the present document highlights that some risk management	Noted. Each MA has a dedicated risk

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	measures have led to negative impacts. It concerns either the ban of antibiotic growth promoters in the EU or some national restrictions of therapeutic antimicrobial use. These negative consequences include deterioration in animal health and substantive increase in the use of some antimicrobials to face clinical infections. Moreover it is clearly stated in conclusion on Question 4 (line numbers 1584-1585) that “Banning the use of specific substances may lead to increase selection pressure on the remaining antimicrobials, and thereby speed development of AMR”. It is important to take into consideration such risk when defining risk mitigations options. As an example (developed in specific comments below), restriction of use for 3rd and 4th generation cephalosporins by intramammary route, while not providing a significant reduction of antimicrobial resistance risk (for reasons explained in specific comments due to the intramammary route specificities), would lead to an increased risk of therapeutic failure by using former generation antibiotics and subsequent increase of antibiotics consumption.	assessment Negative impacts listed in the answer are not intended exhaustive but a list of possible negative impact of measures.
3	The BSAVA realise that the remit of the questions was to assess the impact of the use of antibacterials in veterinary species on human health but would also suggest that consideration needs to be given to the impact of the use (or restriction of use) of antibacterials on animal health, both directly in terms of access to treat bacterial disease and indirectly in terms of responsible use to maintain efficacy for the future.	Noted.
3	**Comments on the answer to the second request from the EC (ranking of antibiotics):** The BSAVA support the proposal from AMEG on the ranking as many of the antibacterials used in companion animal practice are classified as critically important under the current WHO classification in order to allow veterinary surgeons in practice to make responsible choices in practice, while still enabling access to the range of	We agree that treatment guidelines need to be updated on a regular basis. The text has been updated accordingly.

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	antibacterials needed to maintain animal health and welfare through the treatment of bacterial disease. We acknowledge that other classes of antibacterials commonly used in veterinary practice (e.g. certain penicillins, with efficacy against the enterobacteriaceae) and aminoglycocides may also have a higher risk of introducing antimicrobial resistance (category 2). However in determining the potential risk to public health we ask that the risk from antibacterial use in food producing animals and companion (non-food producing) animals be considered separately. It will also be important to ensure that before restrictions are introduced on the use of certain antibacterials that there are suitable products (e.g. formulation, tablet size) available for to enable all species and conditions to be appropriately treated. With respect to the production of treatment guidelines, we agree that a number of factors need to be considered when making decisions to use antibacterial treatment, and note than in companion animals these decisions will need to include the individual circumstances of the owner. We also agree that any guidelines produced should be evidence based and take account of local knowledge about disease causing organisms and their sensitivity. However we also recommend that any guidelines need to acknowledge that these factors will change over time and that any recommendations for antibacterial use will in itself affect the resistance patterns encountered and lead to the need to update any guidelines on a regular basis.	
3	**Comments on the Answer to the third request from the EC (new antibiotics):** The BSAVA support the idea of risks assessments for new substances or classes of antimicrobial and agree that this should focus on this risk of transfer of resistance of relevance for public health from treated animal. However, we would suggest that the risk of transfer of resistance should be considered separately for food producing and companion (non-food producing) animals as the risks involved may be very different.	Agreed but no further action needed. For traditional zoonotic organisms like Salmonella, Campylobacter and VTEC the transmission from animal to man is normally foodborne, i.e. different from companion animals in which direct

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		contact with owners is of concern. Livestock associated MRSA is nevertheless an example of an occupational hazard with direct zoonotic transfer from the (food producing) animal to people. The traditional distinction between foodborne and food producing animal-borne thus is no longer possible. The document yet makes on several occasions a clear separation in categorisation of antimicrobials and assessment between companion animals and food producing animals. The overall conclusion on Q4 specifically is focused on food producing animal species.
	With regard to the possibility of future legislation to allow banning or limitation of off label use in animals for certain antimicrobials/classes authorised only in human medicine, the BSAVA recognise that this may be necessary but recommend that any hazard characterization or risk assessment should include not only the risk of antimicrobial resistance to public health but also the risks to animal health and welfare and potential increase risk of zoonotic disease if substance is withdrawn.	Point noted. In the present document, no exhausting listing of all elements that should be taken into consideration are listed. Sentence proposal change: "… a benefit risk assessment concluding that there is an acceptable level of risk relating to resistance in bacteria (or resistance determinants) of relevance for public health in relation to the benefit for animal health and welfare is required."‥

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	As we noted in our response to an earlier consultation one of the main indications for use of human licensed products in companion animals is for the treatment of zoonotic disease, for example Azithromycin Psittacosis (birds), *Chlamydophila felis* in cats and Clarithromycin as part of combination treatment protocol for mycobacteria as well as in the treatment of *Nocardia* and *Actinomyces*.	Table is changed accordingly: Azithromycin – Birds – Psittacosis Azithromycin – Cats – Chlamydophila felis Clarithromycin - ~~Cattle~~, fowl, horses and pets ~~sheep~~ - Various, including respiratory infections, (e.g. combination therapy for *Mycobacterium* spp.), *Nocardia, Actinomyces* spp. Agreed and clearly stated in the document, no further action needed here.
	The BSAVA would support the introduction of a declaration system in order to assess the extent and evolution of off label use of human only authorised antimicrobials and will work to develop systems to make this possible in practice. The BSAVA also support the proposal for Marketing Authorisation Holders to monitor susceptibility to new antimicrobial products. We would suggest that these are not only	Agreed. Sentence added: *"These regularly updated databases preferably should also be consultable for practitioners to enable them to take account of this information in their*

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	made available to the regulatory authorities but also to practitioners to enable them to take account of this information in their prescribing.	*prescribing and approach during unexpected relapse."*
3	**Comments on the Answer to the fourth request from the EC (risk mitigation options):** It is out with our remit to comment on risk mitigation appropriate to veterinary use of antimicrobials in food producing animals but again would suggest that risk management is appropriate to the species and circumstances, and that measures put in place with regard to food producing animals are not automatically applied to companion animals. Any decision to restrict the use of antibacterial products should be based on sound evidence.	The overall conclusion on Q4 specifically is focused on food producing animal species.
4	FVE would congratulate the EMA on this opinion, which we believe covers all important matters in a balanced way and which in general we can support. **Answer to Question 2** FVE believes the categorisation by AMEG into the 3 groups is rational and makes good sense. One point of attention is that the document suggests that treatment guidelines need to be locally created and implemented rather than developed at EU level. While FVE can see the reasoning behind this (different species, husbandry conditions, diseases and climate), the danger is that certain regions will be more restrictive than others, which allows for uneven competition and can lead to changing livestock production especially of young animals to countries with less strict treatment guidelines. From the point of the prescribing veterinarian, another issue that should be taken into consideration has to do with the order that the different pieces of guidance should be	Thank you very much for your comment. With regard the different order that the different pieces of guideline it is not with

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	followed, i.e. whether the SPC or treating guidelines or any other legal rules should take priority. **Answer to Question 3** FVE can support the answer given to question 3. We suggest changing the order and slightly the text of the recommendations in question 3. Please write: *Line 23: Put in place a declaration system in order to assess the extent and evaluation of off label use of human only authorised antimicrobials* *Line 235: If necessary, include in future legislation flexible tools to allow banning or limitation of off label use in animals of certain antimicrobial classes authorised only in human medicines following a hazard characterisation and risk-benefit assessment.* We suggest the same change on page 39 line 996-1014. As illegal import is important to recognise, we suggest also making reference to this in the summary answer made (now is only included in the detailed answer- line 902-905). One aspect we miss is that veterinary practitioners use scientific publications as one of the resources to update themselves. It is a concern that some of these publications occasionally refer to the use of antimicrobials only licensed for human use and even	the AMEGs remit to give any further details as the legal base on treatment guidelines will differ in each countries *Agreed to change order, not agreed to change sentence (– mentioning the evolution and not 'evaluation' is considered necessary for the benefit-risk assessments).* Agreed to change order. Sentence changed into: '*Include in future legislation flexible tools to allow banning or limitation of off label use in animals for certain antimicrobials/classes authorised only in human medicine following a unfavourable hazard characterization or risk assessment'* A footnote has been added in the summary on illegal import. It is out of the remit of AMEG what should be published. The cascade should be applied

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	recommend them sometimes. We believe a recommendation should be included that this should be avoided. **Answer to Question 4** The response to question 4 is quite narrow sided. It only looks at use of antibiotic use in general and of specific classes. It does not take into account other risky practices, such as movement of animals, mixing of animals, improvements that can be made by better biosecurity, import of animals and products from third countries, etc. As FVE commented previously, we believe that more than imposing further mitigation measures, priority should be given to adherence to the currently available risk mitigation measures and effective stewardship of veterinary antibiotics. We also should not forget the global and one health character of antimicrobial resistance. Regulation of antibiotic prescribing and use in Europe is already the most stringent worldwide. Yet it must be recognised that despite the best efforts in Europe humans, animals and products travel, and can possibly carry resistance with them. Any mitigation measure in the animal field should always reflect on similar measures in man. • Promoting responsible use in the rest of the world! There is no benefit if we keep on raising the standards for farming in the EU while we import animal derived products produced in lower standards. • Promoting Sensitivity testing as a daily practice • Put in place and enforce herd health visits. Every farm should have a proper herd health management plan, which includes regular animal health visits by the veterinarian in order to prevent diseases. • Promoting responsible ownership and educate pet owners to consult their veterinarian regularly. • Making the veterinary prescription compulsory for all antibiotics. Any	responsively according to AMR. The point is outside of the scope of AMEG. Where human products are used, it should be done responsibly. Scope of response clarified. Above practices considered to outside remit of question. Noted.

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	antimicrobial should always be administered only after examination and (laboratory) diagnosis and according to the veterinary instructions. For certain classes of antimicrobials (CIAs) administration should be restricted to veterinarian only. • Supporting targeted training on responsible use of medicines. • Promoting Statutory compliance (such as through Veterinary Code of Conducts) • Promoting recording and monitoring of consumption on farm as well as on vet level • Promoting an ethical industry (promotion, licensing avilomycin in Turkey, …) • Preparing the appropriate framework that will allow control of the sale of antibiotics on Internet. It is inconsistent to discuss restraining veterinarians from using certain antimicrobials, while leaving the window open for anyone to easily access the medication they need on - line, even without veterinary examination, diagnosis, veterinary prescription or any other control (see FVE position on Internet sales). In addition, we feel the scientific evidence and background data on the effectiveness of risk mitigation measures are very weak. Difficulties in estimating the impact of risk management measures are acknowledged in the answer on question 4(see line 275-281), but should be more prominently noted in the answer. We suggest moving line 275 to 281 to after line 263. Also very important is the decision on key 'measurements of success' and desired outcomes for an effective policy. This should also be more prominent in the summary answer.	This has been made clear in the document. Further research has been recommended. No further action considered necessary.
5	The document is very balanced in terms of maintaining veterinary medicinal products to treat livestock (including pigs) and not banning complete antimicrobial families to be used in livestock. Obviously, this option is feasible if a prudent use of antimicrobials is carried out during the daily practice. We agree with almost everything included in the document. The only point that must be discussed in more detail is the classification of	Noted. AWP is currently working on reflection paper on aminoglycosides and extended spectrum penicillins.

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	antimicrobials. Right now, some members of the beta-lactam family, such as amoxicillin, and aminoglycosides are included in Category 2 (risk for public health is high) because more studies are needed in order to classify them as Category 1 (low risk for public health) or Category 2. It seems very reasonable to maintain aminoglycosides and some members of the beta-lactam family as Category 1 unless it is scientifically demonstrated that they must be classified as Category 2. A number of goals would also be useful to help understand the impact of antimicrobial use in pigs on antimicrobial resistance development and spread to man. 1. To know how many milligrams of antimicrobials are needed to rear a pig of 100 kg body weight in each European country. This data is available for the veterinary species as a whole (ESVAC, 2013) but there is no data only for pigs. 2. To know exactly which antimicrobials are used for each clinical condition in pigs throughout Europe. Moreover, it must be specified a prophylactic, metaphylactic or therapeutic use of antimicrobials. Until now, there is a scarcity of information about this topic. 3. To promote the determination of antimicrobial susceptibility to common pathogens throughout Europe following standard methods accepted internationally (CLSI; 2013 or EUCAST). 4. To revise the guidelines of prudent use of antimicrobials with a focus on pigs at European level.	AWP work program: http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2013/01/WC500137231.pdf Concept paper on use of aminoglycosides: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/07/WC500170029.pdf ESVAC project is currently starting a pilot project collecting data from pig farms[1] See above Initiative has been taken place at EU level to collect target pathogens in a harmonised level

[1] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp&mid=WC0b01ac0580153a00&jsenabled=true

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	5. To quantify the risk of spread of resistant organisms and genes on a species basis from animals to humans. 6. Last but not least, it would be important to emphasize that the removal or restrictions on antibiotic usage can also be a double-edged sword, since to leave animals without medication in order to reduce its use may cause a significant lack of animal welfare	
7	The British Veterinary Association (BVA) is the national representative body for the veterinary profession in the United Kingdom and has over 14,000 members. Its primary aim is to protect and promote the interests of the veterinary profession in this country, and it therefore takes a keen interest in all issues affecting the veterinary profession, be they animal health, animal welfare, public health, regulatory issues or employment concerns. Whilst we recognise that the purpose of this response is to provide advice on measures to manage the possible risk to humans, it is important, for both animal welfare and public health, that veterinary surgeons have access to antimicrobials which are effective in treating bacterial disease in animals.	Noted.
8	• EPHA agrees that acknowledging the importance of antimicrobial agents in medicine, and the possibility of spreading resistance from animals to humans, is vital when creating treatment guidelines for veterinary use. • EPHA advocates promotion and implementation of a holistic ''One Health'' approach in the fight against AMR. Human and animal health is intimately linked. • EPHA agrees that specific treatment guidelines cannot be established at EU level due to national and regional differences. This does however not preclude development	No action considered necessary.

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	of overarching recommendations on prudent use of antibiotics that would be applicable anywhere. • EPHA welcomes the idea of categorising antimicrobials as this may help to decrease risk for animal and public health.	
9	1. The UK Advisory Committee on the Microbiological Safety of Food (ACMSF) welcomes the above report and particularly the AMEG proposals to: 1.1 Place antimicrobials from the WHO CIA list in three different categories for veterinary use. This is particularly welcome in light of the recent appearance in food-producing animal species in some EU Member States of bacteria with the ability to hydrolyse carbapenem antibiotics, which are regarded as 'last- resort' antibiotics for the treatment of infections with multiple drug-resistant bacteria in humans. In this respect it is reassuring that carbapenems should remain as an antibiotic classified as a Category 3 antimicrobial; 1.2 Recommend that a specific risk assessment for each new substance or new class of antimicrobial is needed to assess the risk of transfer of resistance of relevance for public health from treated animals; 1.3 Include in future legislation flexible tools to allow banning or limitation of off- label use in animals for certain antimicrobials/classes authorised only in human medicine following a hazard characterization or risk assessment, and to put in place a declaration system in order to assess the extent and evolution of off-label use of 'human only' authorised antimicrobials. In particular, the ACMSF regards the off-label use of antibiotics as a major obstacle in ensuring responsible use in countries where prescription data are not collected as it is difficult, if not impossible to quantify and	Noted and appreciated.

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	control; 1.3 Recommend monitoring of the cascade use of antimicrobials indications , with option to introduce restrictions in such usage if considered necessary; 1.4 Include fluoroquinolones and 3rd_ and 41h-generation cephalosporins as antimicrobials of special concern, in light of their importance in human medicine, and possibly to implement legislation for their usage in veterinary medicine. 2. The ACMS F also commends the AMEG on recognising the importance of such factors as: the organisation of non-chromosomal resistance genes into horizontally-transferable elements enabling localisation of resistance determinant s on DNA outside the bacterial chromosome on such elements as conjugative or mobilisable plasmids, transposons and integron-gene cassettes, thereby promoting transfer of resistance genes within and between bacterial species by a variety of methods; the presence of plasmid addiction systems, which have only been relatively recently observed and which are being increasingly identified in a range of bacteria . and which may be of major importance in stabilising resistance plasmids in the absence of antibiotic selective pressure; the importance of co-and cross resistance in the spread of resistance genes; and the possible role of commensal organisms as reservoirs of resistance genes which may be transferred to pathogenic bacteria under the influence of selective pressure. 3. The ACMSF similarly commends AMEG on the range of new risk management options proposed under Question 4, and the recognition of the importance of measuring antibiotic consumption in animals in EU Member States and changes in resistance patterns that may relate to changes in usage patterns.	

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	4. The ACMSF recognises that foods are a method of spreading drug-resistant bacteria and resistance genes therein from food production animals to humans. As such the ACMSF considers that insufficient emphasis has been placed in the AMEG report on the occurrence of resistance in foods and the environment, and identification of the pathways for dissemination of drug-resistant organisms and resistance genes from animals to food. For example, precise figures for the occurrence of resistant bacteria in foods in many EU Member States are not available, nor is information about, e.g., the overall occurrence of drug-resistant commensal organisms in the human population and particularly in persons associated with food production, such as farm workers, abattoir staff, and food handlers in the retail food industry. The ACMSF would therefore welcome a statement about the necessity of further research •into pathways of dissemination of drug-resistant - bacteria, whether pathogens or commensals, from food animals to humans, and also research into methods and quantification of the spread of resistance genes from commensals to pathogens in foods and the environment.	Added as a new bullet point in 2.11: *"Further research on pathways of dissemination from animals to food and into methods for the quantification of the spread of resistance genes from commensals to pathogens in foods and the environment "*
	5. Although not specifically referred to in the Report, the ACMSF would like to-comment on the increasing use of epidemiological cut off values (ECOFFs) as a measurement of resistance, and the extrapolation of ECOFF results from food animal-derived bacteria to human infections . Although ECOFF's and clinical levels for the treatment of infections in humans are similar, or even identical, for many antimicrobials, this is not the case for certain .'drug/bug' combinations - e.g., fluoroquinolones/Sa/mone//a (should treatment be indicated) . As such, expression of resistance. to fluoroquinolones at ECOFF levels .from cases of infection in humans can be misleading and may result in treatment problems. As not everyone is aware of the difference between ECOFFs and clinical breakpoints, ACMSF would encourage EMA and others to highlight this issue in future reports to help interpretation of susceptibility data.	Noted.

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11	IFAH-Europe is grateful for the opportunity to comment on this draft response. Industry fully supports the principle of the responsible use of all antibiotics and believes this is an important tool to preserve their efficacy for the future. We agree with the emphasis AMEG has placed on risk assessment. However, it is very important that the requirements for risk assessment are realistic and include parameters for which the interpretation is clear; e.g. data on antimicrobial resistance can be very difficult to interpret and depends on many factors. All requirements for such a risk assessment should be discussed and clarified in a separate document, which would undergo the normal consultation process. We note that in lines 818-820 it is mentioned that "CVMP are working on further guidance on the conduct of risk assessment for antimicrobials where the focus is on the risk to public health". Hopefully, this document(s) will address our concerns. IFAH-Europe agrees that access to new classes of antimicrobials could benefit from an early hazard characterization exercise. To be of most value this assessment should be carried out early in the development process and would therefore probably be based on bibliographic, in-vitro data and early pharmacokinetic data. We would wish that such activity be reflected in the recent legislative proposal of the EU Commission on veterinary medicinal products. The development and implementation of evidence-based treatment guidelines as opposed to prescriptive formularies is supported. Evidence/science/clinical judgement for the respective indication must be the guiding principle. We are also in agreement that a categorization of antibiotics at EU level should not result in pan-European treatment guidelines. It is absolutely critical to realise that a treatment guideline should be based on the best benefit/risk balance (including all benefits and risks) and clinical judgement; not just on AMR risk. Lastly, it should be noted that formularies and treatment guidelines may be	The CVMP is currently drafting a guideline on risk assessment. We agree that a hazard characterisation could be advantageous when conducted early in the development process. However the detail for this procedure will be outside the remit of this group.

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	contradictory to the strict use of veterinary medicinal products according to the SPCs as sometimes active ingredients are included on an off label basis in formularies/treatment guidelines. In this situation neither the clinical benefit nor risks will have been assessed by the appropriate regulatory authority. This trend is counter to the principles of the regulation of veterinary medicines and should be resisted.	
	It is appreciated that among the factors influencing the possible transfer of antimicrobial resistance to humans from the use of antibiotics in animals, the route of administration is often cited (in answer to Question 2 and Question 3). It highlights that antimicrobial categorisation should not be pre-emptive of a risk assessment; and that risk management measures should take into account the various factors in the chain of events from the use of antimicrobials in animals to possible antimicrobial resistance issues in humans (line number 404/ figure 1), among which is the route of administration in animals.	See comments and replies above. Route of administration is clearly mentioned in the document.
	In the answer to Question 4, the present document highlights that some risk management measures have had negative impacts. We agree with this and believe the possibility of potential negative impacts should be considered prior to implementation. Overall, we are left with the impression that the current document predominantly focuses on the current situation and is taking a very cautious and restrictive approach – which cumulatively may compromise (licensed) medicines availability. In the response to the third question, we welcome the proposal for a risk assessment at an early stage as a potential way forward, however no other options are discussed and the main focus of that response is on off-label use. A clear and overarching vision for future developments and innovation in the area (existing and new products, including alternatives) and potential incentives seems to be lacking. This vision should span the longer term horizon (20+ years in the future) given the long time required to develop novel substances and products, and the potential for animal pathogens to develop resistance to existing substances. Last but not least, it should ensure continued	Noted.

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	availability of properly licensed antibiotics to treat infectious diseases in animals in a responsible way. We believe that many elements of this vision and the need for innovation are already present in the document; they only need to be strengthened and presented in a more concise manner.	
12	En avril 2013, la Commission européenne a demandé un avis à l'Agence européenne des médicaments (EMA) concernant l'impact sur la santé publique et animale de l'utilisation d'antibiotiques chez les animaux, ainsi que sur les mesures de gestion pour le risque possible chez l'homme. Les autorités françaises (AF) souhaitent apporter des commentaires sur les réponses de l'EMA. En premier lieu, les AF saluent les recommandations suivantes : - Imposer une analyse de risque de l'antibiorésistance en amont d'une demande d'autorisation de mise sur le marché (AMM) d'un nouvel antibiotique vétérinaire et réévaluer le risque d'antibiorésistance pour les AMM d'antibiotiques existants; - Inclure dans le futur règlement relatif aux médicaments vétérinaires des outils permettant des restrictions, dans le cadre de la cascade, sur l'usage d'antibiotiques uniquement autorisés en médecine humaine ; - Évaluer de façon plus systématique et efficiente les usages d'antibiotiques à usage humain dans le cadre de la cascade. En second lieu, les AF souhaitent apporter les commentaires suivants : - Concernant la méthodologie de classification des substances antibiotiques, la liste de l'OMS telle que publiée en 2011 n'a pas été prise en compte intégralement (cf paragraphe à partir de la ligne 450 du document) ce qui conduit à ne pas classer certaines substances comme les céphalosporines de	Thank you for your comments. See answers in the specific comments.

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	1ère et 2ème génération et ne facilite pas l'interprétation de cette catégorisation au plan pratique par les EM. - Concernant les génériques, les AF saluent la recommandation visant à imposer une évaluation de risque en amont de la demande d'autorisation de mise sur le marché pour tout générique d'antibiotique. Elles **regrettent qu'aucune recommandation n'ait été émise pour les génériques d'antibiotiques vétérinaires contenant des molécules pour lesquelles le risque pour la santé publique est actuellement élevé** (fluoroquinolones et céphalosporines de 3 ème et 4ème génération) Concernant **l'usage des antibiotiques vétérinaires contenant des aminosides et certaines pénicillines à spectre étendu associées aux inhibiteurs de béta-lactamases, les AF souhaitent que leur profil de risque soit établi de manière prioritaire,** en raison de l'utilisation importante de ces molécules en médecine vétérinaire et du risque élevé de transfert de résistance.	Changes have been made in the concerned section (Q3). See comments above on aminoglycosides and extended spectrum penicillins.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
195	2	**Comment:** The route of administration should also been taken into account for treatment guidelines as it has an impact on antimicrobial resistance. **Proposed change (in bold) :** … at the class, substance, **route of administration** or even at the indication level.	Accepted.
327 (Table 1/ Category 2)	2	**Comment**: Whereas the text lists in Category 2 "systematically administered (parenteral and oral) 3rd- and 4th-generation cephalosporins" (lines 174 and 354), Table 1 does not specify the concerned routes of administration for these antimicrobials. As 3rd- and 4th –generation cephalosporins are also used by intramammary route in dairy cows, such specification appears necessary, based on scientific and regulatory rationale : i) **Scientific rationale**: Main issue concerning the use of 3rd- and 4th-generation cephalosporins in human and animal health is the emergence of Enterobacteriaceae strains producing Extended Spectrum Beta-Lactamases (ESBL). Use in dairy cows by intramammary route should be considered apart in the risk assessment of these compounds as explained below from the example of cefquinome medication by this route of administration at the time of drying off. This use is allowed in a number of European countries through different marketing authorizations (Pioneer drug : Virbactan®/Cephaguard® DC – Generics : Cefquinor® DC/Cefimam® DC). The comments developed below will follow the different steps of possible impact of such use on the emergence of ESBL producing Enterobacteriaceae strains,	Noted, this is why risk assessment is always needed at product level. The factor 'route of administration' is explicitly mentioned in the document as important factor in assessments.

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		namely : 1) Potential impact on mastitis pathogens 2) Potential impact on treated cow digestive flora 3) Potential impact on digestive flora for a calf ingesting colostrum from a cow treated at drying off **1-Potential impact on mastitis pathogens** Most recent data from French surveillance network (Résapath, 2012 survey) show a very high susceptibility rate of Enterobacteriaceae to cefquinome when strains are isolated from mastitis milk samples. These figures are identical to that recorded during a French survey in Rhône-Alpes region between 2007 and 2008 (Botrel et al 2010). In the Résapath survey, susceptibility rate of *Enterobacteriaceae* to cefquinome is still high but lower when strains are isolated from diarrhoeic calves (Table 1). Thus diarrhoeic calves appear to be the quasi-exclusive source of ESBL producing *Enterobacteriaceae* in cattle. **Table 1 : Susceptibility to cefquinome of French *Enterobacteriaceae* strains isolated in 2012 (Résapath 2013)** **Origin** / **Species** / **Number of strains** / **Susceptibility (%)** **Mastitis** / ***Escherichia coli*** / **559** / **99** **Mastitis** / ***Klebsiella pneumoniae*** / **52** / **100** **Diarrhoea (calves)** / ***Escherichia coli*** / **2754** / **87**	

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		At the European level, the most recent survey performed by the European Center for Animal Health Studies (CEESA) shows similar data with a susceptibility rate of 98.6% (290/294) to cefquinome (in lack of international norms for cefquinome susceptibility breakpoints, recommendations from the Antibiogram Committee of the French Society for Microbiology (CA-SFM) are taken into account). These data were obtained from a collection of Enterobacteriaceae strains (Escherichia coli and Klebsiella pneumoniae) isolated from mastitis cases in Europe between 2007 and 2012 (QBAS 2013). A genetic molecular study confirmed a very low rate of ESBL producing Enterobacteriaceae strains (6/1427 i.e. 0.4%) from a collection of French mastitis strains isolated between 2009 and 2011. Interestingly, a plausible human origin of the ESBL producing strains was evoked, reinforced by the known close contact between farmers and cows during the milking process (Dahmen et al 2012). Very low resistance rate of mastitis pathogens is explained by udder features (usually sterile gland unfavourable to genetic exchanges between bacteria contrarily to digestive tract) and specificities of intramammary antibiotic treatment (full dose poorly resorbed). Thus the risk of transmission of resistant bacteria from milk or milk products to humans is very limited, even in case of raw milk consumption (Botrel et al 2010). **Conclusion**: Intramammary use of cefquinome at drying off since 10 years (first marketing authorization granted in France in march 2004) has not led to the emergence of mastitis resistant strains. Moreover this particular use of cefquinome does not present any risk of transmitting resistant factors from	

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		cows to humans through milk. Obviously it is of utmost importance to pursue the follow-up of mastitis pathogens susceptibility pattern to cefquinome. **2-Potential impact on treated cow digestive flora** Evaluation of this impact is based on cefquinome resorption study after intramammary administration. Indeed an eventual effect on digestive flora requires the antibiotic resorption followed by digestive elimination. Following administration of a cefquinome ointment to 6 dairy cows according to label use (one 150 mg cefquinome tube per quarter at drying off), no cefquinome could be quantified in plasma from 4 h to 21 days after treatment. Taking into account regular plasma samples timing and low threshold of validated HPLC/UV plasma assay (limit of quantification equal to 30 ng/mL), intramammary resorption of cefquinome during dry period can be considered as negligible (Ehinger et al 2005). **Conclusion**: Due to negligible resorption of cefquinome from intramammary infusion at drying off, impact on digestive flora can be considered as nil for the treated cow. **3-Potential impact on digestive flora for a calf ingesting colostrum from a cow treated at drying off** Milk residue studies are performed in order to recommend a withdrawal time for human consumption. However various reports have raised the concern of waste milk, i.e. milk from treated cows during this withdrawal time, which may be distributed to calves (CVMP 2009, ANSES 2014). In the case of antimicrobial treatments, such waste milk containing drug residues may impact calves digestive flora. A recent survey in 557 UK dairy farms showed that 83 % of	

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		respondents used waste milk to feed calves (Brunton et al 2012). This practice should be discouraged as being at risk of generating antimicrobial resistance. Nevertheless the particular case of colostrum must be considered. Indeed the colostrum is vital for newborn calf immunity. But inactivation of eventual antibiotic residues is not possible without degradation of immunoglobulins. Thus a significant degradation of Ig G is noticed from colostrum heating at 63°C (Mc Martin et al 2006) whereas such heating has a minimal effect on beta-lactams used in drying off tubes (Roca et al 2011). Therefore it is necessary to assess if antibiotic residues are present in the colostrum from cows treated by an intramammary specialty at drying off and if such residues (if any) could impact the calf gut flora. Such evaluation is performed for cefquinome hereunder from milk residue study carried out for Marketing Authorization of the pioneer drug and taking into account the determination of cefquinome Maximal Residue Limits (MRLs). In the milk residue study, 29 dairy cows were administered cefquinome at drying off by intramammary route (one 150 mg cefquinome tube per quarter). Individual milk samples were taken on each milking during the first 5 days after calving. Cefquinome concentrations were assayed in colostrum or milk by a HPLC/MS validated method with a quantification limit of 10 µg/L. All concentrations were below the MRL (20 µg/L), maximal concentration being equal to 15 µg/L, and even mostly below the limit of quantification (10 µg/L) from first milking (Ehinger et al 2005). Therefore the **20 µg/L** value can be considered as a threshold value which will never be achieved in colostrum.	

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		Thus the remaining question is to assess if a concentration below 20 µg/L in colostrum can have any impact on digestive flora of a calf receiving such colostrum. To answer this question, an estimation of oral intake is firstly determined. As the recommendation of colostrum intake during the first day of life is around 10% of body weight (i.e. 5 L for a calf weighing 50 kg at birth), the cefquinome oral intake can be estimated as being **lower than 2 µg/kg** during the first day of life (20 µg/L x 5 L/50 kg). This intake can be compared to the Acceptable Daily Intake (ADI) which has been defined for human consumption prior to determination of cefquinome MRLs. Indeed the ADI takes into account a microbiological ADI covering potential effects on the human gut flora : disruption of the colonization barrier and increase of the resistant bacteria population (EMA 2012b). For cefquinome, the ADI has been set to 3.8 µg/kg (CVMP 1999). It corresponds to the oral daily intake over a lifetime without any side effect in humans, including effects on digestive flora. Thus the estimated cefquinome intake by a calf from colostrum ingestion during the first day of life (< 2 µg/kg) is lower than 53% of the daily intake considered as without effect on digestive flora in humans if it was ingested during the whole life. Such intake from the colostrum is therefore considered as without effect on calf digestive flora. This assessment has been completed by an in vitro study to test if the maximal cefquinome concentration in colostrum following treatment at drying off may impact the susceptibility level of commensal digestive Escherichia coli strains. For this, 10 strains from the CEESA collection (bovine E. coli strains isolated	

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		from healthy animals at slaughter) were selected as being representative for their susceptibility level to 4th generation cephalosporins. Minimum Inhibitory Concentrations (MICs) of cefquinome against these 10 strains were determined before and after exposition 10 times to either a cefquinome concentration of 15 µg/L (maximal concentration measured in colostrum) or to broth only (repeated passages design). Following the 10 passages, cefquinome MICs were mostly unchanged and identical between the cefquinome exposed and control strains (Table 2). The difference of final MICs between exposed and control groups was not significant (p=0.34, paired Student test). **Table 2 : MICs of cefquinome against 10 strains of bovine commensal *Escherichia coli* before and after exposition 10 times to a cefquinome concentration of 15 µg/L (LGC 2014)** **MICs (µg/mL)** / **Range** / **MIC_{90}** **Initial MIC** / **0.03-0.12** / **0.06** **Final MIC (control)** / **0.06-0.12** / **0.06** **Final MIC (cefquinome exposed)** / **0.06-0.25** / **0.06** ***Conclusion**:* Both residue data and *in vitro* test on bovine commensal *E. coli* strains show that the risk of inducing antimicrobial resistance through the	

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		colostrum of a cow treated with cefquinome by intramammary route at drying off can be considered as negligible. **General conclusion on scientific rationale** Data presented in the above comments show that intramammary use of cefquinome at drying off does not risk inducing the emergence of resistant bacteria and particularly ESBL producing *Enterobacteriaceae*. This is a demonstrative example of Virbac opinion that the classification of 3rd and 4th generation cephalosporins in Category 2 of Table 1 should exclude the intramammary use. ii) **Regulatory rationale** : The reference cited in the EMA document (line 659) about SPCs prudent use warnings concerns only systematically administered 3rd and 4th generations cephalosporins in food producing animals (EMA 2012a). The same definition has been taken into consideration for inclusion of these compounds in Category 2 (lines 174 and 354), thus excluding the intramammary route from the scope of such categorisation. **Proposed change in Table 1/Category 2 (in bold): systematically administered (parenteral and oral)** 3rd- and 4th-generation cephalosporins	
1499 (Table 6/ Responsible use warnings)	2	**Comment:** For the reasons exposed in above comment to Q2 answer (line 327 Table 1/ Category 2), the concerned routes of administration should be specified for 3rd and 4th generation cephalosporins) **Proposed change (in bold):** …included for fluoroquinolones and **systematically administered (parenteral and oral)** 3rd- and 4th-generation	See above. References to the referrals for fluoroquinolones and 3rd and 4th generation cephalosporins have been added.

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		cephalosporins following referral procedures…	
1592 and 1595	2	**Comment:** The term “cephalosporins” is more general than “3rd and 4th generation cephalosporins” mentioned in line 1591 and the route of administration is not specified. For the reasons exposed in above comment to Q2 answer (line 327 Table 1/ Category 2), the following change is proposed. **Proposed change :** replace “cephalosporins” by “**systematically administered (parenteral and oral)** 3rd- and 4th-generation cephalosporins” **References** ANSES. Avis relatif aux risques d’émergence d’antibiorésistances liés aux modes d’utilisation des antibiotiques dans le domaine de la santé animale (Advice on the risks of antimicrobial resistance emergence linked to the modes of use of antibiotics in animal health). Saisine n°2011-SA-0071, rapport d’expertise collective, janvier 2014. Botrel M.A. et al. Distribution and antimicrobial resistance of clinical and subclinical mastitis pathogens in dairy cows in Rhône-alpes, France. Foodborne Pathogens and Disease 2010, 7, 479-487. Brunton L.A. et al. A survey of antimicrobial usage on dairy farms and waste milk feeding practices in England and Wales. Vet. Rec. 2012, 171, 296. Dahmen S. et al. Characterization of extended-spectrum beta-lactamase (ESBL)-carrying plasmids and clones of Enterobacteriaceae causing cattle mastitis in France. Vet. Microbiol. 2013, 162, 793-799. Committee for Veterinary Medicinal Products. Cefquinome Summary Report 1999, EMEA/MRL/005/95.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Committee for Veterinary Medicinal Products. Revised reflection paper on the use of 3rd and 4th generation cephalosporins in food producing animals in the European Union: development of resistance and impact on human and animal health. 2009, EMEA/CVMP/SAGAM/81730/2006. Ehinger A.M. et al. Pharmacokinetic aspects of a new dry cow therapy. Cattle Practice 2005, 13, 227-230. European Medicines Agency. Opinion following an Article 35 referral for all veterinary medicinal products containing systematically administered (parenteral and oral) 3rd and 4th generation cephalosporins intended for use in food producing species. EMA/967448/2011. January 2012a. European Medicines Agency. VICH GL36(R) : Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI. EMA/CVMP/VICH/467/2003. May 2012b. LGC. MIC testing of cefquinome against 30 *E. coli* strains, with subsequent sub-inhibitory MIC passage against 10 *E. coli* strains. Analytical report 2014. McMartin S. et al. Heat treatment of bovine colostrum. I: Effects of temperature on viscosity and immunoglobulin G level. J. Dairy Sci. 2006, 89, 2110-2118. QBAS (Quotient Bio Analytical Sciences). MIC determination of the VetPath III collection of veterinary bacterial pathogens from Europe. Final analytical report 2013. Résapath. Réseau d'épidémiosurveillance de l'antibiorésistance des bactéries pathogènes animales. Bilan 2012 (Epidemiological survey of animal pathogens antibioresistance. 2012 survey). Edition scientifique octobre 2013. Roca M. et al. Effect of heat treatments on stability of beta-lactams in milk.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		J. Dairy Sci. 2011, 94, 1155-1164.	
208-227	4	**Comment**: As illegal import is important to recognise, we suggest also making reference to this in the summary answer made (now is only included in the detailed answer- line 902-905) **Proposed change**: Add reference to illegal import as in lines 902-905.	See above.
235- 239	4	**Comment**: We suggest changing the order and slightly the text of the recommendations in question 3. **Proposed change**: Begin line 235: • *Put in place a declaration system in order to assess the extent and evaluation of off label use of human only authorised antimicrobials* • *If necessary, include in future legislation flexible tools to allow banning or limitation of off label use in animals of certain antimicrobial classes authorised only in human medicines following a hazard characterisation and risk-benefit assessment*.	See above.
263-281	4	**Comment:** We suggest line 275 to 281 to be moved after sentence in line 263. **Proposed change:** *…in other Member States (MSs). Difficulties in estimating the impact … they will be measured.*	Agreed.
860	4	**Comment:** Within the veterinary field, the use off-label of antimicrobials for	Insufficient evidence is available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		use only in human medicines is perceived as very low, as notified by the report only in seldom rare cases in companion animals. **Proposed change:** Change 860-862 to: *In the veterinary field, the extent of use of antimicrobials for use only in human medicines is estimated to be rare and only very occasional in companion animals. No quantitative data are available.*	
996-1024	4	**Comment:** See comments above. **Proposed change:** *Move Lines 1008-1024 above in the place of lines 996 – 1007 and change the introductory sentence as following*: • *Put in place a declaration system in order to assess the extent and evaluation of off label use of human only authorised antimicrobials* *Move Lines 996 – 1007 below in the place of lines 1008-1024 and change the introductory sentence as following*: • *If necessary, include in future legislation flexible tools to allow banning or limitation of off label use in animals of certain antimicrobial classes authorised only in human medicines following a hazard characterisation and risk-benefit assessment.*	Agreed. See also comments above.
1516	4	**Comment:** this sentence is not correct. The price is a factor which practitioners take into account but of much lower importance than other factors such as sensitivity tests, own experience, the risk for antibiotic resistance developing and ease of administration.	No change.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: *According to a survey amongst veterinarians in Europe by the Federation of Veterinarians of Europe published in 2013, price is a factor of lesser importance, in relation to other factors such as sensitivity tests, own experience, the risk for antibiotic resistance developing and ease of administration.*	
1623	4	**Comment:** not only the economic consequences should be looked at, but also the health and welfare consequences **Proposed change:** *Change sentence slightly to "Researching methodologies to evaluate the potential economic, health and welfare consequences involved for both human and animals, that would result from the introduction of new risk-based measures*"	Accepted.
165	5	**Comment**: It is suggested that the pleuromutilins are included alongside the macrolides **Proposed change**: Category 1. Certain penicillins, macrolides, pleuromutilins, tetracyclines and polymyxins belong to this category.	Please note that the question from the Commission concerned compounds and classes listed as CIAs by WHO. Pleuromutilins is not listed and thus out of scope for this task.
326	5	**Comment**: Pleuromutilins (tiamulin and valnemulin) should be included in Table 1, in Category 1. **Proposed change**: Include pleuromutilins in Table 1 Category 1. Under Antimicrobial class - Pleuromutilins Under Zoonotic hazard – Campylobacter spp Under probability of resistance – Low Under Veterinary medicine – Approved (including group medicine)	In principle we agree with this comment but it was not considered in the framework of this document that focuses on the CIA according to WHO.

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		Under Concluding remarks – Compliance with responsible use principles is necessary to reduce risk.	
202-203	5	**Comment**: 'treatment guidelines need to be locally created and implemented rather than developed at EU level.' This conclusion is supported	Noted.
1429-1430	5	**Comment**: 'Despite the ban of antimicrobial growth promotion from 2006, the use of preventive antimicrobial courses still persists.' Currently, prevention claims are valid indications in the EU. Some growth promoters, which were not under veterinary prescription or control also had disease prevention effects. Approved products can be used legitimately for prevention and are done so by veterinarians who perceive a high disease risk if they are not included. e.g. Strep suis as mentioned but also post-weaning diarrhoea associated with Escherichia coli if products like zinc oxide are not permitted. This has resulted in the extensive use of colistin in some countries. The EU has to decide whether preventive use is acceptable or not as an indication and do not confuse it with growth promotion. A further consideration put forward by some stakeholders was that if pigs have to wait for treatment when the herd is known to be infected with Actinobacillus pleuropneumoniae, this will cause significant mortality in finisher pigs, respectively. Thus, there are some pig diseases such as porcine pleuropneumonia where a prophylactic or metaphylactic use of antimicrobials is totally justified. **Proposed change**: Delete 'Despite the ban of antimicrobial growth promotion from 2006,'	See above Agreed. Next text added: *"The use of antimicrobials for routine or systematic prevention of disease is of concern. There was a ban of antimicrobial growth promotion in 2006. However, systematic preventive use of antimicrobials is routinely practised in some intensively reared livestock."*
1450-	5	**Comment**: In addition to the cost of disease associated with Strep suis and	Agreed, text modified accordingly.

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1455		estimated at €60 million, which is endorsed a similar mortality figure of 2% could be put on post-weaning mortality due to E. coli if left untreated with zinc oxide or colistin. A ban on prevention use could affect 95% of pig farms and a cost of €190 million could be estimated. This explains why vets and farmers require to be able to use antimicrobial substances at times of known high risk situations. **Proposed change**: Insert 'A similar mortality figure of 2% could be put on post-weaning mortality due to E. coli if left untreated with zinc oxide or colistin. A ban on prevention use could affect 95% of pig farms and a cost of €190 million could be estimated.'	
1499	5	**Comment**: In Table 6. Possible regulatory risk management measures, under section SPC restrictions at reducing exposure to the antimicrobial there is consideration of 'No prophylactic use' and 'No metaphylactic use.' This is considered to have a detrimental effect on the health and welfare of animals under the care of the veterinarian. Currently, a definition of prevention and metaphylaxis has not been given by the EMA and the Guideline is still under consultation. It is considered dangerous to propose such changes before they are defined. This could have an effect on a number of products that have the legitimate indication of prevention. It is not thought that any product has a specific metaphylactic claim as such in the EU. **Proposed change**: It might be better to remove Prophylactic use and Metaphylaxis from the table.	See above.
1499	5	**Comment**: In Table 6. It also discusses the possibility of restrictions from use	Not agreed. The table addresses a broad

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		as mass treatment for herds and groups of animals. Treatment of individual animals only. This is impractical especially when you may be dealing with thousands of animals. Very few farms would have the manpower or money to treat and handle whole herds of pigs by injection, especially as they grow beyond the weaner stage up to 100kg. **Proposed change**: It might be better to delete Herd/flock and group treatments.	range of possible risk management measures for different species. The text has been modified to make clear that those are possible options. New heading: *"Possible options for regulatory risk management"*
1499	5	**Comment**: In Table 6. In Dosing regimens, administration it describes 'Restriction from use as formulations that prevent accurate dosing for individual animals e.g. in feed or water.' Again while dealing with large numbers of animals it is almost impossible to rely on injections only. It is impractical and costly and potentially hazardous to the administrator. It is not surprising therefore in the pig world, antibiotic administration in most countries is most commonly given in feed, on feed or via the drinking water. **Proposed change**: Remove 'Restriction from use as formulations that prevent accurate dosing for individual animals e.g. in feed or water.'	Not agreed. See comment above.
1570-1581	5	**Comment**: Beyond one Canadian study there is no direct evidence for potential beneficial effects to human health of these risk mitigation measures or that any of these proposed changes will have any direct effect on human antimicrobial resistance. It is surprising that the effects of voluntary or compulsory withdrawal of cephalosporins for use in food animals in several EU MSs have as yet not been assessed. Wouldn't this be a good thing to do to prove that these potential measures might have some impact?	We agree that the effects of the withdrawn of cephalosporins in some MSs should be investigated and published. We believe that this is currently been investigated in some countries.

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1582-1583	5	**Comment**: 'Negative effects of the withdrawal of cephalosporins in slaughter pigs include reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaners with oedema disease.' This is incorrect it was thought to be due to the introduction of the Yellow card system in Denmark and restrictions of use of all antimicrobials. (Alban et al, 2013). **Proposed change**: 'Negative effects of the introduction of the Yellow card system in Denmark for pigs include reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaners with oedema disease.'	Response: Change made. New text: *"Reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaners with oedema disease."*
1602-1603	5	**Comment**: 'Despite the ban on growth promoters, many compounds are still given by the oral administration route for preventive purposes.' It is not despite the ban of growth promoters it is because of the ban of growth promoters that many therapeutic antibiotics are used for prevention. **Proposed change**: 'Because of the ban on growth promoters, many therapeutic compounds are given by the oral administration route for preventive purposes.' **References**: Alban, L., Dahl, J., Andreasen, M., Petersen, J.V. and Sandberg, M. (2013) Possible impact of the 'yellow card' antimicrobial scheme on meat inspection lesions in Danish finisher pigs. Preventive Veterinary Medicine, 108, 334-341 DANMAP 2006 (2007) Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in	The text has been amended to avoid confusion. *"The use of antimicrobials for routine or systematic prevention of disease is of concern. There was a ban of antimicrobial growth promotion in 2006. However, systematic preventive use of antimicrobials is routinely practised in some intensively reared livestock."*

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		Denmark. Section: Antimicrobial consumption in animals, pp 17-22.	
177-183 663-680	6	**Comments:** Aminoglycosides do include some antibiotics widely used in Vet, FPA. e.g. Streptomycin, Neomycin, Gentamicin. EGGVP would appreciate further detailed information on the procedures to perform "further risk profiling" to these substances mentioned by EMA.	See comments above on aminoglycosides.
282-283 1504 – 1509 1524-1525 1600 - 1602	6	**Comments:** In several paragraphs it is stated that the increased availability of generics has contributed to large increases in usage levels because of a **lowering of costs** (1) and **increase of marketing activities** (2). Regarding the first issue, the Heads of Medicines Agencies and the Federation of Veterinarians of Europe recently undertook a survey De Briyne et al. (2013) to gain a better insight into the decision making process of veterinarians in Europe when prescribing antibiotics. In this survey, involving over 3000 veterinary practitioners from 25 European countries, the contrary was true; economic factors were the least important factors in their prescribing behaviors. Responses indicate that no single information source is universally considered as critical, and training, published literature and experience were the most important parameters that determined the choice of an antibiotic. Factors recorded, which most strongly influenced prescribing behaviour, were sensitivity tests, own experience, the risk of developing antibacterial resistance and ease of administration. Regarding the second issue, statistics available at EU and National Authorities indeed show that the number of generic marketing authorizations have steadily increased during the last few years in Europe, but this had not led to an	Not agreed. Strong evidence on human medicine cannot be neglected. A recent publication from ANSES confirms the text: Chauvin, C., 2009, Impact of generic introduction on antimicrobial usages - A time-series analysis. J. Vet. Pharmacol. Ther. 32, 111-112 https://www.anses.fr/sites/default/files/documents/ANMV-Ra-Antibiotiques2008.pdf

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		increase of overall antibiotic consumption in recent years. This is demonstrated in the conclusions of the third ESVAC report: From 2010 to 2011 a considerable decrease on the use of antimicrobials was observed in most EU member states. EMA conclusions on the generics 'impact on antimicrobial use do not do not take those the references into consideration, but are based on these 3 references: 1. Monnet, Ferech, Frimodt-Moller, & Goossens, 2005: *The More Antibacterial Trade Names, The More Consumption of Antibacterials: A European Study* 2. Jensen et al., 2010: *Effect of generics on price and consumption of ciprofloxacin in primary healthcare: the relationship to increasing resistance* 3. Toutain & Bousquet-Melou, 2013: *The consequences of generic marketing on antibiotic consumption and the spread of microbial resistance: the need for new antibiotics* EGGVP is concerned by the fact EMA has based its opinion on these 3 publications. Firstly, because these (Monnet et al., Jensen et al.) refer to studies performed in human medicine. The scope of the third publication (Toutain et al.) remains unclear, as it refers to both human and veterinary medicine. The fact that these are not veterinary references makes the publications not suitable to draw conclusions on the veterinary side. Human and veterinary medicine run under **completely different economic models**. Primary healthcare service and structure as well as insurance reimbursement policies are exclusive from human medicine. Furthermore, the price of medicines is not regulated in veterinary medicine, as it is in human. Also the ***approaches and attitude of prescribing veterinarians and doctors*** are not comparable. Regardless the influence of price in prescribing	

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		habits (not being a major factor in veterinary medicine as already cited above), the management and treatment orientations are very different in human and veterinary medicine: pathologies and indications are different, in veterinary there are many species and categories to be taken into account, human medicine is oriented to individual treatments, while herd treatment is common in veterinary n vet treatment of many individuals… Also the level of responsibility of a doctor towards human patients can influence its approach when prescribing an antimicrobial. Behaviours and practice of a veterinarian treating a herd and a human doctor treating a human individual are far different. The ***review article from Toutain et al***. deserves a specific mention. EGGVP has prepared a reaction to it with the objective to clarify some of the statements provided by the Authors and also to raise some critical questions. The basis for EGGVP's reaction is summarized below: • Ambiguous approach, possible misinterpretations • Omission of relevant references • Statements not correct from an EU perspective • Unsupported statements, lack of evidence, Author's opinion EGGVP's reaction has been accepted for publication at the Journal of Veterinary Pharmacology and Therapeuthics (13 August 2014), and will soon be published in this Journal in the form of a letter to the Editor. In the meantime, we invite EMA to have a detailed look at EGGVP's arguments, as a full copy of the EGGVP reaction is available in our website: http://www.eggvp.org/news For the reasons stated above, we believe that **the 3 publications cited by EMA as a basis to draw conclusions on the impact of generics in the use**	

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		of antimicrobials are not appropriate. We would instead recommend taking into consideration: - the HMA/FVE survey regarding prescribing habits from veterinarians, which show that the possible price erosion produced by generics is likely to have very little influence in the prescription pattern of veterinarians, and - the ESVAC reports and the statistics available at EMA and HMA, showing that the number of generic marketing authorizations has increased during the last few years in Europe, but this had not led to an overall antibiotic consumption in recent years. The basic role of generic medicines is substitution, not to increase use. The veterinarian will prescribe the antibiotic when it is needed, regardless the type of marketing authorization (generic or originator). If there is not generic, the antimicrobial will be used as well (originator). Reccommendation to EMA: to remove all references to generics associated to an increase of use (or to include appropriate references to justify this statement)	
852 (Table 4)	6	**Comments:** In the Table 4, Metronidazole is inserted as one of the medicines that are only used in human medicine and used off label in animals. The compound is used off label in dogs, cats and horses for treatment of chronic diarrhoea and clostridium infections. For precision, it might be worth mentioning that metronidazole is one of the active ingredients of the product Stomorgyl (by Merial) which is authorised in several member states and indicated for treatment of oral conditions in cats and dogs.	Agreed, metronidazole has been removed from the table 4.

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981-988	6	**Comments:** One of the recommendations on Question 3 is considered with risk assessment of new antimicrobial substances for use in food producing species. The reinforcement of such assessment is recommended. An early hazard characterization/abbreviated risk assessment is recommended. It may be beneficial to include recommendation to provide some more detailed guidance for such procedures. This should allow early detection of the hazard and assessment of related risks. Thus, it would prevent unnecessary procedures (incl. animal experiments) and costs in development of medicines, which could later be found of too high risk for authorisation and use.	See comments above.
1324 (Table 5)	6	**Comments**: EGGVP has been informed of some recent measures applied in Germany. This could be added to the table. http://www.wattagnet.com/169756.html?utm_source=KnowledgeMarketing&utm_medium=Enewsletter%20Groups&utm_term=Poultry%20Update&utm_content=14_08_21_Poultry%20Update_Thursday&utm_campaign=German%20poultry%20farmers%20face%20antibiotic%20scrutiny	Agreed, added under chapter 2.5: *"Germany - Goals to reduce overall use of antimicrobials by benchmarking with other farms are been implemented."*
1510-1513	6	**Comments**: EMA report includes the following example: "At least six generic versions of ceftiofur came on the market in the UK following the expiration of marketing exclusivity. This led to large reductions in price, to increased marketing, including advertising directly to farmers. The result was a five-fold increase in usage of modern cephalosporins over 10 years when there was no clinical justification for increased use." Some parts of this statement are not precise. Reference to source of data provided would be welcomed. Is there any data that the reference product was always used as recommended (clinically justified) and that the principles of	The text has been amended.

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		prudent use were respected when using the references but are not for the generic products? It would also make sense to know if this increase was related to reduction of other antibiotics use to have a complete picture?	
1519-1522 1513	6	**Comments**: A recommendation is made to require a new AMR risk assessment at the time of application for a generic product. There may be various difficulties related to risk assessment for any antimicrobial product (several factors should be considered for the proper risk assessment and some may be difficult to obtain, e.g. estimation of exposure/use in any particular category of animals vs. sales data; there may be different resistance patterns in different regions). Furthermore, the applicant might not be aware of concurrent submissions which would make estimations of future exposure even more difficult. Hence, some more detailed guidance on the issue would be welcomed.	The sentence has been deleted :"A new RA should be required at the time of application for a generic product" It is added: *"Based on the outcome of the AM resistance surveillance and usage a new RA could be required for all products of a specific AM class incl. generics and reference products."*
157-193	7	**Comment**: We agree with the AMEG categorisation into 3 groups which we believe is rational and makes good sense. We support the emphasis on responsible use principles in everyday practice for all antimicrobials (even low risk or Category 1). We also support the restrictions for category 2 antimicrobials, i.e. that they should be used only when there are no alternatives, and this is consistent with BVA responsible use guidance and the position taken by the Federation of Veterinarians of Europe (FVE). The call for certain penicillins which are effective against Enterobacteriacae to be risk assessed to see if they should be regarded in the same way as	See previous comment (CVMP is currently making a risk profile) The categorisation is provisional one, it is not implied automatically that restrictions will apply. Categorisation should be regularly reviewed/updated by CVMP and CHMP

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		fluoroquinolones and cephalosporins seems reasonable. Those listed in Table 2 and put into category 3 as recommended for human use only, and animal use exceptionally also seem sound. It should be noted that potentiated amoxicillins are the most commonly used antibacterials in small animal practice. Although we support responsible use in these products, there would need to be alternatives put in place before any restrictions were implemented. This is particularly important in terms of injectable products for dogs and cats, where if potentiated amoxicillins and fluoroquinolones were restricted, there would be few authorised products left. Whilst some of the predominantly farm animal products, e.g. Engemycin, are licensed for use in dogs and cats, their formulation and bottle size make their use impractical.	
195-204	7	**Comment**: We agree with the principle that treatment guidelines need to be locally created and implemented rather than developed at EU level. Guidelines should be evidence based and take account of local knowledge about disease causing organisms and their sensitivity and should be reviewed on a regular basis. Where products are used without a marketing authorisation specific to the circumstances, as is the case virtually all the time with goats in the UK, then the legal liability of any person or organisation setting out either rules or recommendations needs to be clarified first. A number of our specialist divisions have produced sector specific treatment	No action considered necessary.

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		guidelines (e.g. BEVA) or guidance to help practices develop their own policies (e.g. BSAVA).	
208-245	7	**Comment**: We support the approach taken in answer to the third request.	Noted and appreciated.
259	7	**Comment**: The paper makes reference to restrictions in place in Scandinavia and the Netherlands. We do not support such restrictions in the UK. Looking at DANMAP 2012, the incidence of multi-resistant E.coli has actually increased in pigs and poultry. It is of paramount importance that any decision to restrict the use of antimicrobial products be based on sound scientific evidence. Any risk assessments should be appropriate to the species and the circumstances. In principle, we support the monitoring of sales of antimicrobials at the veterinary level and we note that the Veterinary Medicines Directorate have been exploring how monitoring might be conducted in practice. We await their findings with interest. We note that there could be difficulties in determining use in some production animals on farms which are mixed species enterprises (e.g. beef and sheep), and medicines supplied are being used across species. Interrogation of individual farm medicines records could be laborious.	Noted. No action considered necessary.
582-585	8	**Comment**: The use of antimicrobials may be reduced considerably without impact on animal health. **Proposed change**: Promotion of Good Farming Practices and animal	In principle we agree but we find it less appropriate to expand on this topic in this paragraph. To fully cover this topic a separate paper would be needed and we

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		husbandry can serve to avoid infections and prevent AMR spreading via air, water and soil. Research has also shown that certain food production systems (i.e. organic) are associated with lower levels of AMR and hence create less dependency on antimicrobials. There are several non-antibiotic approaches to the treatment and prevention of infection (e.g. probiotics, phages, phytomedicines) but the scientific evidence base is still unclear. The growing field of complementary and alternative medicine (CAM) comprises numerous treatment options for the prevention and treatment of health conditions that can support the move away from the current state of over-prescription of antibiotics.	find this out of scope of the current task.
811-815	8	**Comment**: The authorisation of completely new classes of antimicrobials for use in animals only may decrease public health risk. Proposed change (if any): Research should be encouraged for developing and testing novel antimicrobial therapies that are not susceptible to developing microbial resistance.	Agreed, the following sentence has been added: "Research also should be encouraged for developing and testing novel antimicrobial therapies that are not susceptible to developing microbial resistance."
957-960	8	**Comment**: ESVAC proposed monitoring system to estimate antimicrobial consumption by data collection, but excluding off label use. **Proposed change**: Data about off-label antibiotics for use in animals must be collected and thoroughly assessed. This should be a public health obligation.	In the text: "Prescribers should keep records of off label use to be provided at the request of the Authorities." – it already covers this comment Added: *"Authorities should be encouraged to collect off label use data."*

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1032-1059	8	**Comment**: Analysis on classes of antimicrobials that are authorised for use in human medicine and not in veterinary medicine. **Proposed change**: It will help to minimise the public health risk related to antimicrobial resistance derived from animal husbandry. There should be classification for antibiotics that can be used without risk and for those that should only be used in exceptional circumstances due to their high risk of spreading AMR.	This addition is unnecessary. The current list has been made as far as possible. Any use under the cascade should be under exceptional circumstances.
1324-1444	8	**Comment**: Examples of risk management measures that are considered as a positive or negative impact on health. **Proposed change**: EU Member States should be encouraged to learn from countries including Denmark, Sweden, Finland and the Netherlands which have already introduced regulations requiring veterinarians to perform microbiological examinations and susceptibility testing before prescribing antibiotics.	Noted.
1503-1518	8	**Comment**: Increased use of generics because of low price and advertisement directed to farmers resulted with increased use of cephalosporins (not recommended for first line of treatment). **Proposed change**: The overall opinion about generics is that they are equivalent to the original product, i.e. their quality, effectiveness and safety are the same but for a lower price. Marketing of generics should however be kept at a minimum to decrease use of certain drugs.	The text has been amended in 2.9.

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325	10	**Comment**: Category 1 is supposed to group antimicrobials where the risk for public health is currently estimated low or limited. This is not the case for macrolides that are first line therapeutics for numerous human infections, especially in children and pregnant women where fluoroquinolones cannot be used or for infections with fluoroquinolone-resistant Campylobacter. In addition, they present a high probability of resistance transfer. Furthermore, macrolides are categorized by the WHO as highest priority critically important antimicrobials, as well as fluoroquinolones, 3rd and 4th generation cephalosporins and glycopeptides. Consequently macrolides clearly should be classified in category 2.	Based on the information in the macrolide reflection paper and the recommendations from CVMP, we propose to keep macrolides as Cat 1.
453	10	**Comment**: In L453 it is stated: "The list is not exhaustive as some classes/substances on the WHO list but of less importance for human medicine in EU are omitted." We think all classes used in veterinary medicine should be listed in table 1 (L325) and table 3 (L521). All the more if this categorisation is considered as one element when deciding when/whether to use a certain class/compound in veterinary medicine or when deciding on risk mitigation activities (L190ff).	The Commission specifically requested us to limit the task to compounds/classes of importance for human medicine in EU.
501	10	**Comment**: The Reference of Rawlings, 2006 is missing in Annex V.	The reference has been deleted.
781	10	**Comment**: Monensin should be added as a new antimicrobial active substance authorized in the EU for use in veterinary medicine (centralised authorisation procedure).	Monensin is authorised against ketosis. Last sentence of paragraph changed into: "It should be noted that other AMs may have been authorised using other routes than the Centralised Procedure and that agents with anti-infective

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			activity can be authorised for non-infectious indications (e.g. monensin for ketosis). Administration of the latter compounds will also exert an antimicrobial selection pressure. ”
789	10	**Comment**: Colistin is also one example that should be mentioned here. Colistin use in human medicine was limited to ophtalmic and topical use with the exeption of cystic fibrosis patients until the emergence of e.g. carbapenem-resistant Klebsiella pneumoniae.	Agreed, text changed accordingly.
806	10	**Comment**: For the indication bovine interdigital dermatitis and particularly for the indication bovine respiratory disease (Pasteurellaceae & Mycoplasma), several antimicrobial veterinary products are authorized. A good treatment strategy besides the use of antimicrobials should take into account the various management factors contributing to the development of the disease.	Noted.
847	10	**Comment**: (Table 4). The list of antibiotics that have been used off label in animals sould be amended. For example rifampicin is widely used for the treatment of infections caused by methicillin-resistant Staphylococcus pseudintermedius in dogs (Müntener et al. 2012. Schweiz Arch Tierheilkd. 154:127-128); Vancomycin is being used in horses (Orsini et al., Can J Vet Res. 2005 Oct;69(4):278-86) and Amikacin in dogs (Bloom, Vet J. 2014 Feb;199(2):217-22. doi: 10.1016/j.tvjl.2013.11.014. Epub 2013 Nov 23):	The table has been updated.

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852	10	**Comment**: Much to our surprise we find that the use of Clarithromycin in food producing animals like cattle, pigs and sheep seems to be an (off label) topic in the EU (no MRL established, several authorised vet-products for the indication respiratory infections)!	Cattle, pigs and sheep were deleted from table 4 as target species for Clarithromycin.
1065	10	**Comment**: Risk mitigation options: To minimise the use of (critically important) antimicrobial substances in food producing animals without rising the morbidity and mortality rate, concurrent measures should be taken to improve animal husbandry, hygiene, animal transport conditions etc.. These factors should be mentioned when discussing risk mitigation options.	Accepted. The following text added: *"The answer primarily focuses on the use of such antimicrobials in food producing animals. Measures put in place with regard to food producing animals may not be automatically applied to companion animals. Furthermore practices such as the movement of animals, the mixing of animals, biosecurity aspects of animal husbandry, and the import of animals and animal feed from countries out with the EU, all of which may impinge on AMR, are considered to be outside the remit of the answer."*
1446	10	**Comment**: Cost estimates: We recommend to consider additionally the estimated savings resulting from the reduced usage of antimicrobials and the concurrent reduced treatment costs. On the other hand additional costs might result from undertreatment of animals and the concomitant impact of zoonotic bacteria in humans. However a benefit in societal costs results from the reduction of bacterial resistance in veterinary and human medicine. Direct and indirect costs of environmental	Considered to be outside remit of document. Lines added: *"Direct and indirect costs of environmental pollution resulting from antimicrobial usage are considered to fall out with the scope of this document and have not been taken into account, nor*

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		pollution resulting from antimicrobial usage are not taken into account (Kemper, DOI: 10.1016/j.ecolind.2007.06.002; Mompelat et al,Environ Int. 2009 Jul;35(5):803-14. doi: 10.1016/j.envint.2008.10.008. Epub 2008 Dec 19).	*have additional costs that might result from under-treatment of animals and the concomitant impact of infections with zoonotic bacteria on human health."*
167-168	11	**Comment:** IFAH-Europe supports responsible use for all antibiotics based on science and clinical judgement.	Noted.
174-176 355, 651	11	**Comment:** Potential alternative antimicrobials should only be those authorized for the respective target species and indication. Note that in some MS, there is a tendency to develop formularies based on active ingredient, irrespective of approved indications, and where off-label use is promoted. Such practices render the MA procedures including referrals superfluous and bypass any proper risk assessment and management process. **Proposed change:** These reserved antimicrobials should be used only when there are no alternative antimicrobials authorized for the respective target species and indication that could be used.	Accepted: added in I. Summary and II. Summary: *"authorized for the respective target species and indication"*
194-205 381, 547-607	11	**Comment:** The development and implementation of evidence-based treatment guidelines is supported. However, evidence/science/clinical judgement for the respective indication must be the guiding principle. **Proposed change:** This categorisation may be considered as one element when creating treatment guidelines but a number of other factors need to be considered, some of them regionally. However, evidence/science/clinical judgement for the respective indication should be the guiding principle wherever possible.	We principally agree but do not see a need to change the text. The concerned bodies creating treatment guidelines should know to be evidence based. It would be out of scope to specify this in this context.

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216-218, 229-234 896-901 981-991	11	**Comment:** It is unclear, whether the proposed early hazard characterization refers to all new antimicrobials or only those for use in food producing species. To be of most value this assessment should be carried out early in the development process and would therefore probably be based on bibliographic, in-vitro data and early pharmacokinetic data (prior to initiation of a full development programme). We would wish that such activity be reflected in the recent legislative proposal of the EU Commission on veterinary medicinal products.	In line 232 it is written that it is for food producing species This option can be extended to companion animals considering of direct contacts / industry interest.
240-243	11	**Comment:** It is mentioned that MAH holders should have plans in place to monitor for susceptibility in zoonotic and indicator bacteria. However, it should be acknowledged that resistance data can be very difficult to interpret epidemiologically. For instance, there are several examples in the Danish Surveillance system, DANMAP, showing illogical trends, *e.g*. an increase in tetracycline resistance simultaneously with a decrease in consumption. Also, the trends following the cessation of the use of cephalosporins in the Danish swine production this initially in 2010 led to a significant decrease of ESBL at slaughter in 2011, which was followed by an increase in 2012.	Noted.
244 1030-1031	11	**Comment:** Additional renewals (with specific focus on AMR) would only lead to potential elimination of individual product registrations. Similar and generic products would not be removed from the market at the same time. Furthermore, under existing legislation referrals can be initiated to re-evaluate and harmonise (group of) products and in case of serious risk to public health (group of) products can be withdrawn from the market. **Proposed change:** Please delete lines 244 and 1030-1031	Lines were deleted.

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264-270	11	**Comment:** We do not believe this conclusion can be so clearly drawn from the evidence (impact of voluntary ban on 3-4GC) as in many cases a range of other interventions has been applied concurrently – particularly in the Netherlands. **Proposed change:** Rewrite the final sentence as follows: 'While evidence for this has come from studies in Scandinavian countries and the Netherlands, it has to be acknowledged that other interventions such as significant reductions in overall antibiotic use may mean that it is not a simple cause and effect relationship due to the issues of cross- and co-selection (see lines 1197-1200). As yet the effects…'	Not agreed.
282-285 1523-1530	11	**Comment:** This concern is supported. Potential mitigation measures could be the prolonged data protection for antimicrobials as discussed by the EC for the new legislation, mandatory inclusion of all MAH in resistance programmes (*e.g.* TPMP).	Noted.
294-295	11	**Comment:** It is unclear what "sales" means. The addition of special AB classes when it is a program for all antibiotics appears somewhat as a contradiction. The possibility of a comparison of all different classes is very important in an impact analysis. **Proposed change: "**Monitoring by ESVAC of changes in ~~sales~~ use volume for all antimicrobials ~~in particular fluoroquinolones and cephalosporins~~ as a means to measure impact of actions implemented."	Partially agreed. Text modified: *"Monitoring by ESVAC of changes in antimicrobial consumption in particular fluoroquinolones and cephalosporins as a means to measure impact of actions implemented."*
296	11	**Comment:** The population of animals should be taken into account, when calculating the consumption of antibiotics, otherwise countries cannot be compared, and trends will be difficult to interpret. The use of DDDA and DCDA should be mentioned.	Text modified: *"More precise data by animal species/species categories in future ESVAC reports, including eg. the use of DDDA and DCDA."*

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		Proposed change: More precise data by animal species/species categories in future ESVAC reports, including the use of DDDA and DCDA.	
300	11	**Comment:** We would propose that an additional bullet point is added to this list, the promotion of responsible use. **Proposed change:** Promote Responsible Use of Antimicrobials	No action considered necessary
306	11	**Comment:** Restriction of the cascade (*i.e.* strengthening and clarifying the rules with the maintenance of licensed indications as the first choice) for antibiotics is generally supported in the light of promoting responsible use. But, since at the same time the development of new antibiotics and even the development of new indications for existing antibiotics is increasingly discouraged, care needs to be taken that appropriate treatments for diseased animals remain available.	Noted.
301 and 316	11	**Comment:** It is stated that the overall consumption should be reduced. However, this is in itself is not a very good goal. The goal is to reduce/eliminate unnecessary consumption. In Denmark the consumption has now been brought to such a low level, that irresponsible use is suspected, *e.g.* farmers reduce dosages, treat for too short a time *etc.*, to reduce their consumption below the Yellow card limit. Thus, the drive to reduce consumption risks promoting resistance and putting animal welfare at risk. **Proposed change:** It should be added that reduced consumption should be done within a responsible use framework.	No change in the text is needed.
327	11	**Comment:** Antimicrobial categorisation should not be pre-emptive of a risk	We partly agree, although we have tried

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(Table 1)		assessment; and risk management measures should take into account the various factors in the chain of events from the use of antimicrobials in animals to possible antimicrobial resistance issues in humans (line number 404/ figure 1), among which is the route of administration in animals. For example depending on the properties of the antibiotic involved, administration by intramammary, oral, systemic or topical routes could dramatically alter the risk assessment. **Proposed Change:** Please review the associated text in light of the comment above.	to fulfil the task which was to categorise on compound/class level. One of the most obvious examples where the risk level differs with route of administration would be cephalosporins for intramammary use which is currently not restricted. Modified sentence: *"When writing treatment guidelines decisions on appropriate risk management, measures have to be made at the class, substance or even at the indication level and consider also route of administration."*
347 – 348	11	**Comment:** IFAH-Europe supports the need to ensure the adherence to responsible use principles.	Noted.
357-361	11	**Comment:** There is a need to provide clarity on what "further risk profiling" means. What standards and what methodology will be used? Will it be consistent with international standards? Is the intention to publish a reflection paper on these aminopenicillins and aminoglycosides as is already proposed in the recent concept paper? Due to this proposal we suggest classification of aminopenicillins and aminoglycosides in category 1 until this additional risk profiling is completed, at which time the categorisation can be revised if the completed risk profile demonstrates a necessity to do so.	Yes, the intention is to present reflection papers. See comment above on aminoglycosides and extended spectrum penicillins.
419-420	11	**Comment:** IFAH-Europe proposes deletion of the sentence "Another example is tetracyclines which facilitates (*sic*) spread of MRSA in livestock". The paper	Agreed, the sentence has been deleted.

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		quoted (Price, 2012) does not support the sentence. The link of tetracycline use to the spread of MRSA cc398 in animals is a hypothesis presented in the discussion of the paper and is not the research topic of the paper. We see only too often hypotheses presented in the discussion part of research papers being presented as scientific evidence in following papers. **Proposed change:** ~~Another example is tetracyclines which facilitates spread of MRSA in livestock (Price et al., 2012).~~	
428-429	11	**Comment:** IFAH-Europe agrees. However, this point needs to be emphasised more as many parties do exactly that and refer to the WHO list as dogma. **Proposed change:** It is not intended to be used as the sole source of information for developing risk management strategies <u>and such use is inappropriate and misleading.</u>	No change has been made.
450	11	**Comment:** Typo **Proposed change:** Table 1 should be corrected to Table 2	Corrected.
477 – 481	11	**Comment:** "*In general when there is a decrease in the exposure of antimicrobials a decrease in resistance is observed*": This statement does not have references and is not correct. The data from Denmark and NL where there are reduction targets are either inconclusive or still ongoing. **This is a key point and unfortunately many countries and this report are basing their strategies on this incorrect assumption**. Although we do acknowledge there is an attempt to provide some clarity on times when reduction in consumption does not necessarily lead to the consequent reduction in resistance (lines 480-481). The Netherlands has been very successful in reducing antibiotic use; however, the majority of the reduction is actually in a less important class (tetracyclines).	The text is correct and we don't intend to include more details. It is too early to assess the impact of the overall decrease of antimicrobial consumption in some countries.

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		When looking at the MARAN 2014 report (link), the outcome in terms of changes in resistance rates of the dramatic reduction in use is not clear. The summary of the report states the following: "*In 23% of the raw meat samples ESBL/AmpCs were confirmed to be present. Highest prevalence was observed in poultry meat (83%),* ***this was somewhat higher*** *than found in 2012 (73%).****Thirty five percent of turkey meat was found positive (in 2012 this was 29%)*** *while in beef and pork the prevalence of confirmed ESBLs was* ***comparable*** *to 2012 (respectively 5% in 2013 versus 6% in 2012 in pork and 2% versus 1% in beef). Surprisingly, in crocodile meat 4/10 (40%) of the isolates were confirmed ESBL producers. In kangaroo meat (n=11) no ESBLs were detected. The differences in prevalence in meat between 2012 and 2013 may be due to sampling bias that varies between years.* *It can be concluded that antibiotic sales data show a steady and very substantial decrease since the top year 2007. Hence, the policies initiated in 2008 to limit antibiotic usage were highly successful. In 2013 in organisms from all animal species the resistance levels have decreased including a substantial decrease in the occurrence of cefotaxime resistance in E. coli from broilers. In 2013 the prevalence of ESBL/AmpCproducing E. coli was lower in faecal samples of veal calves and pigs at herd level than in 2012.* ***In meat the prevalence of ESBL/AmpC-producers remained stable.*** *This suggests that the reduction of the quantity of antibiotic use in the Netherlands and those to reduce the use of third-generation cephalosporins have resulted in this reverse of trends. This is a very important signal for policy makers, veterinarians and animal producers, that all their constraints to reduce antibiotic use and at the same time maintain animal health in food producing animals* ***does improve the resistance situation in the food chain****."*	

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		The statement in the last sentence seems to be misleading, since consumer exposure to resistant organisms has not decreased. Looking specifically at the data for Salmonella in the report: "*Antimicrobial susceptibility testing in 2013 was performed on 1906 isolates. Table S02 presents MIC distributions and resistance percentages of all salmonella's tested for susceptibility in 2013. Highest levels of resistance were observed for streptomycin, sulfamethoxazole, tetracycline, ampicillin and to a lesser extent ciprofloxacin, nalidixic acid and trimethoprim.* ***The levels of reduced susceptibility to ciprofloxacin and cefotaxime/ceftazidime have increased compared to 2012.*****"** And STEC: "*Over the last ten years, MIC profiles of STEC isolates seem to have* ***a tendency to increase*** *as shown in Figure STEC01. Traditionally, resistance levels in E. coli O157 have been very low. Most striking increases have been noted over the years for tetracycline, streptomycin, sulfamethoxazole, kanamycin and ampicillin. In 2012 resistance levels seemed stable or even decreased, however in 2013 resistance levels for tetracycline and sulfamethoxazole again increased.* ***Remarkable is the occurrence of resistance (4%) to the quinolones (ciprofloxacin and nalidixic acid). This was never seen in former years, in which resistance levels to quinolones were always below 1%***." E. coli in raw meat products of food-animals: *"In 2013, resistance percentages of E. coli isolated from poultry meat are still high, and have increased compared to 2012. This is possibly due to inclusion of*	

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		meat from non-domestic sources (Table Eco 02). Resistance rates of E. coli from beef and pork samples are stable over the years." Looking at the figures on page 146, resistance percentages are rising in 2013 in all species except veal. Enterococci: *Over the years, resistance to the tested antimicrobials appears to have remained* ***relatively stable*** *in E. faecalis with a tendency to decrease for salinomycin. In E. faecium, pronounced fluctuations were observed. Resistance to salinomycin decreased briefly and resistance to ampicillin* ***increased substantially*** *from 2006 onwards from less than 5% to 30.4% in 2013. Vancomycin resistance was not detected*. Note that no enrichment was used. This report clearly illustrates that reduced use doesn't necessarily lead to a decrease in resistance rates by default. **Proposed change:** this paragraph needs to be rewritten to be more balanced and better reflect the available data.	
510 to 520 and Table 3	11	**Comment:** In lines 510 till 517 and 828-832 a number of factors affecting the transfer of resistance from animals to humans are mentioned. Among others dosing route and regime, volume of usage, animal husbandry conditions, consumption habits, environmental factors, processes between slaughter and intake of food also play a role. Moreover, the way by which a grade has been assigned to each class for the different factors is not clear and, could in our view be challenged or even refined within a class, thus leading to a different final ranking for sub classes within the beta lactams.	Already included in the report: *"In addition to the factors above, that for the most part relate only to genetic mechanisms, there are many other factors that may affect the probability of transfer of resistant bacteria or its determinants from animals to humans which reflect the conditions of use of the*

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		Proposed change: A full judgement of risk of transfer should be based on a proper risk assessment, and it should therefore be clarified that Table 3 is indicative of the risk in general, but other factors should be taken into account for a definitive risk assessment.	*antimicrobial substance, e.g. dosing route and regimen, volume of usage, animal husbandry conditions. These must be taken into consideration for a full public health risk assessment."*
513-514	11	**Comment:** These factors ARE being taken into consideration for a full public health risk assessment (Codex Alimentarius, 2009, 2011). The use of the word "MUST" in the original sentence suggests that it is not currently being done and therefore must be done in the future. **Proposed change:** Clarity needs to be provided if the CVMP considers the same risk analysis process can be applied to non-food borne pathogens.	The "must" is correct. It only forces that it has to be done. This is will be further clarified in RA guideline (CVMP).
521	11	**Comment:** Table 3: The scores allocated to different mechanisms are not clear. It results in just two conclusions for the overall probability of resistance transfer as either high or low. Cephalosporins 3rd & 4th generation get a high rating with an overall score of 16; Fluoroquinolones get a high rating with an overall score of 9. This is significantly different and there is no indication where the breakpoint is or different weightings assigned to different headings. The way the data are currently presented suggest a degree of precision that is not appropriate and appears to be heavily based on the precautionary principle. **Proposed change:** The only way to use this assessment is to use binary data, yes/no answer, as it is based on opinion (from footnotes), all be it an "expert" opinion. Or qualitative assessments such as low medium high. A pseudo quantitative scoring system is not appropriate as it will be open to misinterpretation or misuse.	The scoring is explained after the table. The aim of the group was to estimate the row of the risk transfer.
531-539	11	**Comment:** The same descriptions are used for different scores. The scoring	Comment is not understood.

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		system would seem more objective if discriminate descriptors were used.	
541-589	11	**Comment:** This section should contain a paragraph highlighting the need for local guidelines to include considerations of the route of administration and local or systemic distribution of antimicrobials. For example, the same antimicrobial could be given IV, orally, intramammary, or in ear drops and have a different AMR risk profile in each case.	It is clarified above.
543	11	**Comment:** The likelihood of spread of resistance from animals to man as presented in table 2. Please retain the wording of the heading in the table to prevent misinterpretation. **Proposed change:** and the ~~likelihood of spread of resistance from animals to man~~ **probability of resistance transfer** as presented	Agree, text has been changed.
565-566	11	**Comment:** This prudent use guideline document must reflect the conclusions drawn from this scientific advice on key points such as: i) inability to have one size fits all in EU, re. 1st, 2nd & last line treatments; ii) reduction of AB use does not automatically equate to a reduction in resistance *etc.* In addition, it should emphasise that any decision/ strategy should be accompanied by an appropriate risk assessment, rather than indiscriminate use of the precautionary principle.	This is out of scope of our document.
576	11	**Comment:** Typo **Proposed change:** Annex II should be changed to Annex I	The typo has been corrected.
582-585	11	**Comment:** IFAH-Europe agrees with the minimisation of the unnecessary use, consistent with the message, “as little as possible, as much as necessary”.	Text has been changed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		However, to make such a broad and firm conclusion based on data from 1 country, based on 1 year's data, based on data that is not statistically analysed and concluding that no significant impact on animal health is observed, when examples of impact are provided later in the scientific advice report, is overstating the position. **Proposed change:** This sentence needs to be updated to better reflect the available data.	
604-605	11	**Comment:** This recommendation is very vague, what does "taken into account" really mean? As currently written, it gives an open invitation to use the precautionary principle regardless of supplied scientific data. **Proposed change:** Please clarify the expectations and what standards will be used.	Further detail will be given in the guidance CVMP's currently developing on RA.
652-655	11	**Comment:** Whilst we agree with the sentiment to encourage companies to seek MA's for alternative compounds, the level of increase in uncertainty over the last 5 years, further reinforced in this document (reductions, greater risk assessments, avoidance of classes *etc*.), some clarity needs to be provided as to how the EU will "convince" companies to seek new MA's.	This is out of scope of the report
663-668	11	**Comment:** Given their critical importance in veterinary medicine, maintain aminopenicillins and aminoglycosides in category 1 at this stage, unless the future risk profiling would indicate a need to categorize them otherwise.	See above.
673-674	11	**Comment:** This statement is too vague; there is a need to define to what standard the risk profiling will be carried out. It cannot just be the precautionary principle approach.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
771-774	11	**Comment:** IFAH-Europe agrees with this statement of the problem. However, this section fails to address possible solutions to the issue. It is apparent that there is a current and future need for new agents but no recognition of the ability of antibacterial discovery scientists to develop novel agents that have clear separation from human use agents. This section quickly moves to off-label drug use as a means to fill therapeutic gaps. However, this has no real connection with the development of novel agents and all discussion regarding off-label drug use should be moved to a different section. **Proposed change:** We therefore suggest rewriting this section to focus on innovation and new agents and keep discussion of off-label use of human products to the dedicated section.	No additional information has been provided that would allow the group to rewrite his paragraph. The following has been added: *"Research also should be encouraged for developing and testing novel antimicrobial therapies that are not susceptible to developing microbial resistance."*
789-791	11	**Comment:** IFAH-Europe agrees with this statement, colistin is another example. If these substances become severely restricted or banned from veterinary medicine, therapeutic gaps will become more evident, particularly if the hurdles to develop and market new substances/classes are raised to a level where companies are no longer able to invest.	Noted.
795-798	11	**Comment**: If this need is to be met by expanding indications or developing new products, then it is clear that substantial incentives should be in place. **Proposed change:** Add the above sentence to the text.	It is outside the scope
812	11	**Comment:** Typo **Proposed change:** Section 3.3 should be corrected to Section 6.2	The typo has been corrected.
838-841	11	**Comment:** Clearly, the direction of transfer of these resistant organisms has	Not relevant to this document, therefore

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		been from a human source to food-producing animals and more attention should be paid to the prevention of such events. Laurent Poirel, Roger Stephan, Vincent Perreten and Patrice Nordmann, 2014. The carbapenemase threat in the animal world: the wrong culprit. J Antimicrob Chemother, doi:10.1093/jac/dku054: *(Citations:)* *We fully agree that the implementation of surveillance studies aimed to better evaluate and trace multidrug resistance in general, and carbapenem resistance in particular, is crucial in the fight against antibiotic resistance. We also agree that any effort towards a reduction of antibiotic consumption is valuable and must be sustained. However, we believe that the spread of carbapenemase-producing isolates among animals is not the main explanation for their occurrence in humans. Carbapenems are not registered for use in veterinary medicine, even though they may be used in specific circumstances in companion animals or horses when dealing with multidrug-resistant Enterobacteriaceae. This usage, at least in developed countries, remains rare. The occurrence of carbapenemase-producing isolates in companion animals, as for extended-spectrum b-lactamase (ESBL) producers, most probably results from contamination from the animal keeper, who is statistically more exposed to broad-spectrum antibiotics, and in particular to broad-spectrum betalactams, than the animal itself. In this regard, an increasing and irresponsible use of carbapenems in companion animals might contribute to the selection and dissemination of carbapenem-resistant strains, and all efforts to avoid carbapenem use in veterinary practice should be pursued.* *The real threat related to carbapenemase resistance in humans comes from two*	no action considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		main facts. *The first corresponds to the increased consumption of carbapenems worldwide, as a consequence of an increased rate of resistance to broad-spectrum cephalosporins among human isolates. Therefore, carbapenems, although being last-resort antibiotics, are now considered to be first-line therapeutic options in certain geographical areas where multidrug resistance is endemic.* *The second main explanation comes from the overall increase in human population movements worldwide, including migration and tourism.* *….* *Rapid identification of carbapenemase producers by using easy-to-handle and affordable techniques will contribute to the recognition of infected and colonized patients at an early stage. This will allow the rapid implementation of isolation and cohorting strategies, and the improvement of antibiotic stewardship to prevent the development of outbreaks. It may also contribute to better identification of the possible dissemination of carbapenemase producers, not only within the human population but also from a human source to animals.* Note that Poirel et al were among the first to describe the occurrence of carbapenem-resistant strains in animals, notably in cattle in France: first at ARAE 2011, Tours, France, and later on as Poirel et al, 2012. Carbapenemase producing Acinetobacter spp. in Cattle, France. Emerging Infectious Diseases Vol. 18, No. 3, March 2012. www.cdc.gov/eid **Proposed change:** Please put these findings in their proper context.	
865	11	**Comment:** Typo **Proposed change:** Table 8 should be corrected to Table 4	The typo has been corrected.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
896-901	11	**Comment:** The only realistic scenario would be an early AMR risk assessment. Companies will not invest in the extensive and highly expensive safety and residue package if there is a risk that MRLs would ultimately be denied based on risk for AMR. **Proposed change:** The complexities of such an early assessment should be explored in the present advice.	See comments above.
922-925	11	**Comment:** Please see the comment to lines 838-841	Not relevant to this document, therefore no action considered necessary.
984-988	11	**Comment:** This early risk assessment should be performed **before** a company starts to develop a product and a consumer safety package.	Noted.
1002	11	**Comment:** What is the suggested mechanism to "predict" high levels of off-label use, misuse and serious abuse? **Proposed change:** please elaborate for the sake of transparency/predictability.	We leave this for other bodies to elaborate on in the future.
1005-1007	11	**Comment:** This is already possible under current legislation **Proposed change:** please differentiate between what is covered by current legislation, and what is not.	With the new legislation we foresee a a more detailed legislative basis but it would not be appropriate to detail legislative aspects in this document.
1019-1020	11	**Comment:** What is the basis for this conclusion? It contradicts statements made earlier in the text; for organisms listed in lines 1016-1017 the gap is real and cannot be covered by the use of products authorized in other species. **Proposed change:** please adapt the sentence.	Agreed, the sentence is amended.
1022-	11	**Comment:** Agreed, but incentives should be realistic and provide true	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1024		encouragement for companies to make the investment.	
1025-1029	11	**Comment:** If a MAH needs to do this on his own, it is cost-prohibitive. Substances could be incorporated into the existing (and approved?) MS/ECDC/EFSA or CEESA-EASSA programmes. To date, human AMR surveillance data only concerns isolates from clinical cases; this can never be comparable to EFSA or CEESA-EASSA data based on isolates from healthy animals. Furthermore, for human isolates, clinical breakpoints are used by ECDC, whereas for animal isolates, EFSA is applying ECOFFs, and again this is not comparable. Finally, even within human AMR surveillance, there is no harmonized methodology or breakpoints. **Proposed change:** please reconsider the wording of the advice to include all MAH not just the pioneer.	This refers to the first authorisation. An applicant can always consider sharing resources.
1030-1031	11	**Comment:** Depending on the implementation, this is another dis-incentive for new substances or classes.	Noted.
1053-1055	11	**Comment:** Note that the answer to Question 2 (see Table 1) specifies the need for risk assessment first.	Noted.
1077	11	**Comment:** We agree that all antibiotics must be used responsibly in both veterinary and human medicine. However, carbapenems are not used in food producing animals. Sporadic findings of carbapenemase-producing organisms in livestock is a 'humanosis' (transfer from a human source, either directly or via the environment) and priority should be given to containing such events if one desires to target the real issues.	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1092-1093	11	**Comment:** Please clarify what is included in the term "non-risk management measures".	Corrected. The new text is: *"Possible further regulatory and non-regulatory risk management measures…"*
1095,1186	11	**Comment: "**Resistance in man" is not really appropriate in the context of a scientific document. **Proposed change:** please use the phrase "resistance in human pathogens"	Corrected. New text is: *"resistance in human pathogens"*
1205	11	**Comment:** Typo **Proposed change:** "resistance ~~of~~ **to** a specific antimicrobial"	The typo has been corrected.
1222-1223	11	**Comment:** Full agreement with this statement. Reduced use is a parameter that is relatively easy to measure, but the ultimate goal should be containment of resistance in both human and animal pathogens. The latter can only be achieved by measures in both human and animal medicine to limit environmental dissemination. There is an urgent need for properly designed surveillance programs using harmonised methodology and breakpoints in human and animal pathogens and commensals, which would enable more targeted monitoring of the resistance situation and any possible effect of measures taken.	Agreed.
1323	11	**Comment:** Typo **Proposed change:** Table ~~1~~ **5**	The typo has been corrected.
Table 5 on page 49	11	**Comment:** Restrictions on the fluoroquinolone-use in the Danish swine production since 2002 is mentioned in lines 290-292. Denmark has a long tradition of eradicating diseases in swineherds, and fluoroquinolones have been the drug of choice for eradicating for *Actinobacillus pleuropneumoniae*.	Not agreed. References haven't been provided.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		However, the restriction has made it almost impossible to use fluoroquinolones to eradicate *Actinobacillus pleuropneumoniae* or even to treat pigs efficiently during acute outbreaks. **Proposed change:** In Table 5 it should in the "negative aspects" column be mentioned, that the ban has made it almost impossible to eradicate efficiently for *Actinobacillus pleuropneumoniae* in Danish swine herds.	
Table 5	11	**Comment:** Section on Advice from Dutch Health Council in 2011: adverse events reported: The Dutch Animal Health Service GD in April 2013 reported that they had seen many more E coli infections over 2012 and a strong increase in the number of dead animals submitted for pathological investigation. Normally in non-weaned pigs, E coli would be around 7% of the total samples seen, but this had risen to >20%. In the last quarter of 2012, the percentages of weaned piglets diagnosed with diarrhoea increased from a general average of 7% to 12%, and the percentage of weaners with oedema disease increased from 5% to 14%. They partly explained this by changes in feed composition but also the strong reduction in antibiotic use. Interestingly, many of the E. coli identified were found to be resistant to the 1st choice antibiotics identified in the Dutch formulary for pigs. (Geudeke, Tijdschrift voor Diergeneeskunde 0881 138 Aflevering 4 1 april 2013) **Proposed change:** add adverse events to table 5, as explained in lines 1416-1424 later on in the document.	Comment agreed, changed accordingly. Text added: *"The Dutch Animal Health Service GD reported many more E. coli infections over 2012 and a strong increase in the number of dead animals submitted for pathological investigation."*
Table 5	11	**Comment:** Section on voluntary ban by the British Poultry Council: Increased mortality reported (Davies, Poultry World; May2013, Vol. 166 Issue 5, p32). Citations:	Comment agreed, changed accordingly. Text added: *"Increased mortality reported."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"*Hook 2 Sisters had reduced antibiotics use by more than 50% over the past two years, and now averaged less than the 15mg/kg retailers were asking of them. A consequence of this was increased mortality. "I've been in this industry for 35 years, and this has been the most difficult year that I can remember for a variety of reasons. (…) Mr Dring said that Hook 2 Sisters had stopped virtually all day-old medication on its broilers in April 2012, and that many flocks had not received any medication during their lives. But mortality had grown to unsustainable levels by October, and a "red, amber, green" risk-based assessment model was employed to determine if a flock needed medication. The model takes into account a number of factors, including previous flock rejects, bird health, seven-day mortality and quality in the hatchery, creating a "targeted response" to disease risk."* **Proposed change:** please add adverse events to table 5	
1332-1338	11	**Comment:** Major reductions in VRE: due to change in methodology, namely no longer using selective enrichment. In reality, there was not such a dramatic change: Heuer et al, 2002. Vancomycin-Resistant Enterococci (VRE) in Broiler Flocks 5 Years after the Avoparcin Ban. Microbial Drug Resistance, Volume 8, Number 2. **Proposed change:** please adapt the text of the section	The reference provided has been added, and the following text added at the end of the paragraph: "However, one publication (Heuer et al., 2002) indicates that such reduction might reflect differences in isolation procedures."
1349-1352	11	**Comment:** See above: methodologies used before and after the ban (selective plating or not) to be checked.	See comments above.
1354-1359	11	**Comment:** Data from the Pig Research Centre, Denmark (April 2014): http://www.pigresearchcentre.dk/Pig%20Production/Use%20of%20antibiotics.aspx :	The reference in the text is to the year 2006. An additional reference has been added (Grave et al., 2006) to support

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"*The Danish Veterinary and Food Administration annually issue maximum limits for antibiotic consumption in three age groups of pigs. The consumption of antimicrobials in pigs is evaluated as animal daily doses (ADD) per 100 animals seen over the last 9 months (by age group). The target was to achieve a 10% reduction in the antimicrobial use in 2013 compared to 2009. This target was met as the use (in kilo active compound) in Danish pig production in 2013 was 13% lower than in 2009.*" Danmap, Statens Serum Institut, Press release 11 September 2013: http://www.danmap.org/Downloads/Press%20releases.aspx Note that this release is only available on the webpage in Danish, not on the one in English: "*Antibiotikaforbruget til dyr har større udsving fra år til år end forbruget til mennesker, blandt andet som følge af en række lovindgreb. Det samlede forbrug af antibiotika til dyr steg med 4% fra 2011 til 2012. Ændringer i forbruget er især forbundet med forbruget i svineproduktionen, som står for 76% af antibiotikaforbruget til dyr i 2012.* ***I 2012 steg forbruget til svin med 6%, regnet i doser, og når der tages højde for, at svineproduktionen faldt, var stigningen reelt på 10% målt i standarddoser per standarddyr****. Stigningen skal ses i lyset af et markant fald i 2011, efter at myndighederne i 2010 indførte en ordning med "gult kort" til svinebesætninger med det højeste forbrug*." (In swine production, an increase of 6% in 2012 expressed in doses, and due to the decrease in swine production, a real increase of 10% in standard doses per standard animal)	the statement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Annette Cleveland Nielsen, DVM, PhD, Chief Veterinary Advisor, Animal Welfare and Veterinary Medicine Ministry of Food, Agriculture and Fisheries of Denmark 2014, trends: http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/pdf/Presentaties%20SDa-symposium/presentation-cleveland-nielsen-sda-symposium-march-2014.pdf Denmark, various media, 21 Feb 2014: http://www.dr.dk/Nyheder/Penge/2014/02/21/0221080315.htm : Gult kort virker ikke: Svin får mere antibiotika (Yellow Card does not work: Pigs get more antibiotics) **Proposed change:** Please adapt the text to reflect official numbers and trends.	
1388	11	**Comment:** Information was provided during the consultation procedure: (Davies, Poultry World; May 2013, Vol. 166 Issue 5, p32) **Proposed change:** Please include the information in this reference.	The information could not be retrieved.
1395-1405	11	**Comment:** Also consider the note in the Advice from the Dutch Health Council in 2011: "*For years, avoparcine was used as an antimicrobial growth promoter in animal feed in numerous countries. Cross-resistance occurs between avoparcine and vancomycin as both medicines belong to the same chemical group. The occurrence of VRE in hospitals and the suspected transfer of resistance from enterococci from food animal production to humans resulted in banning avoparcine as an animal feed additive in the late 1990s, in accordance with the Health Council advisory report.*	No action considered necessary.

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		Subsequent research found that vancomycin resistance in human bacteria demonstrates a complex dynamic, and that the relationship with avoparcine use in food animal production is not as strong as believed at the time. For example, banning the use of avoparcine in animal feed in some cases did, and in others did not lead to the disappearance of VRE from hospitals." Examples of the latter include: **Denmark**: http://www.ssi.dk/English/News/EPI-NEWS/2014/No%2017%20-%202014.aspx : Increasing VRE occurrence in Danish hospitals (EPI-NEWS No 16/17 - 2014) **France**: Bourdon et al, 2011. Changing trends in vancomycin-resistant enterococci in French hospitals, 2001–08. J Antimicrob Chemother 2011; 66: 713–721. doi:10.1093/jac/dkq524 Fournier et al, 2012. Twenty years of antimicrobial resistance control programme in a regional multi hospital institution, with focus on emerging bacteria (VRE and CPE). Antimicrobial Resistance and Infection Control 2012, 1:9. http://www.aricjournal.com/content/1/1/9 **Germany**: Gastmeier et al, 2014. Dramatic increase in vancomycin-resistant enterococci in Germany. J Antimicrob Chemother March 2014. doi:10.1093/jac/dku035 **Proposed change:** To be considered in conjunction with the fact that 5 years after the ban of avoparcin in Denmark, VRE levels in poultry were virtually unchanged when using the same selective plating methodology used by DANMAP before, but not after the ban.	Response: no action considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1410-1412	11	**Comment:** please consider official numbers and trends (see comments on lines 1354-1359)	See comments above.
1416-1424	11	**Proposed change:** add a synopsis to Table 5 for consistency	See above
1429-1430	11	**Comment:** The linkage of preventative use of antibiotics and antimicrobial growth promotion is erroneous and misleading. There are factual differences in the dosing of the antibiotic in feed, in mode of action, in clinical and zootechnical outcomes, in dispensing conditions (prescription). The sentence actually as written implies that the prescriber of a preventative antibiotic has systematically the intention to obtain a growth promoting effect. We are not aware of any survey or data allowing such a supposition to be made. IFAH-Europe does not support the use of routine prevention in the absence of recognized risk factors recognized by the practicing veterinarian. **Proposed Change:** We would propose deletion of the sentence and replace by: "The use of antimicrobials for routine or systematic prevention is a concern."	Agreed. Next text added: *"The use of antimicrobials for routine or systematic prevention of disease is of concern. There was a ban of antimicrobial growth promotion in 2006. However, systematic preventive use of antimicrobials is routinely practised in some intensively reared livestock."*
1430-1439	11	**Comment:** In this section there is a very negative approach to oral medication (flock-medication). Thus, it is said that "oral administration routes lead to a dramatic increase of resistance.", and that "group medication by the oral route continues to exert a substantial selection pressure" and "prophylactic and metaphylactic group medication by the oral route continue … exert… substantial selection pressure". However, this is not always clear: In Pedersen, K.S. et al, 2010. (Estimates of the between pen variation in outbreaks of acute diarrhoea. Proceedings 2. ESPHM (European Symposium of Porcine Health), May 27th - 28th, 2010, Hannover, Germany, p. 123.) it is shown that diarrhoea due to	We disagree, however we recognise that oral route is needed for certain treatments

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Lawsonia is present in all pens within a section, and that it is therefore concluded that it only makes sense to treat whole sections at a time (implying metaphylactic group medication). This is strongly supported by the findings reported by Larsen et al., 2014. (Effect of individual pig, pen-wise and room-wise treatment on faecal shedding of L. intracellularis, Proc. 23rd IPVS), who found that faecal shedding of LI was lowest for room-wise treatment, compared to individual pig or pen-wise treatment. These studies are soon going to be followed up by resistance data, however these are not yet published. Knowing that a short efficient treatment usually leads to less resistance, the above-mentioned results can be extrapolated to say that room-wise oral medication may lead to less resistance, than pen-wise oral or individual parental treatment of pigs against Lawsonia intracellularis. **Proposed change:** The section should also include the beneficial aspects of oral treatments.	
1433-1434	11	**Comment:** Administration via the oral route can indeed lead to an increase in resistance in commensal bacteria, as shown by the references quoted in the lines above. This can also be true for other routes of administration, not just the oral route, and is transient in nature. As written now, the text implies that oral use in animals is directly detrimental to human health; there is no justification for this “jump to conclusion” and is in fact contradictory to the text presented in section 2.2 especially in lines 1186-1190. Note that a vast majority of human antibiotic use is via the oral route, and there too an increase in commensal organisms, as documented by e.g. Fantin et al, 2009 (Ciprofloxacin Dosage and Emergence of Resistance in Human Commensal Bacteria. The Journal of Infectious Diseases 2009; 200:390–8) or Chardin et al, 2009 (Reduced susceptibility to amoxicillin of oral streptococci	We disagree, however we recognise that oral route is needed for certain treatments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		following amoxicillin exposure. Journal of Medical Microbiology (2009), 58, 1092–1097). With this knowledge in mind, it is clear that responsible use of antibacterials is warranted, both in animals and in humans. Administration via the oral route remains important in veterinary medicine, especially for species such as poultry. Its importance in human medicine is also indisputable. **Proposed change:** please revise the text to maintain consistency throughout the document.	
1450-1461 1586-1588	11	**Comment:** The costs to the producer are estimated here, but the costs to governments of implementation should also be considered (i.e. additional laboratory capacity, administration and enforcement).	Agreed but no data available.
1462-1490	11	**Comment:** These findings demonstrate that even a sustained (very) restrictive use of antibiotics in non-extensive livestock production (as compared to conventional intensive farming systems with a higher use of antibiotics) does not result in an absence of resistant organisms in/on animals and once more illustrate the complexity of the issue. **Proposed change:** please add a conclusion to this section	Outside the scope of this report.
1497	11	**Comment:** text references Table 2 **Proposed change:** please change to Table 6	The typo has been corrected.
1499 (Table 6/ Responsible use	11	**Comment:** For the reasons exposed in above comment to Q2 answer (line 327 Table 1/ Category 2), the concerned routes of administration may be specified (for example 3rd and 4th generation cephalosporins). **Proposed change (in bold):** …included for fluoroquinolones	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
warnings)		and **systemically administered** 3rd- and 4th-generation cephalosporins following referral procedures…	
Table 6, second row	11	**Comment:** This is already the case under current legislation, and we are aware of at least one recent instance where approval was denied based on the grounds stated in the right column of Table 6. Generic applications should also be considered in this section. It would be helpful if CVMP could give priority to the development of a new guidance on AMR following the Concept Paper that was released earlier. **Proposed change:** change “new substances” to “new applications”, “should be subject to” into “are subject to” and “should be considered” into “is considered”	Yes, this is currently the case. Nevertheless, in our view, the legislation could benefit from being more clear and detailed regarding AMR related risks. We don’t agree to include generic applications but have made other recommendations in this regard.
Table 6, third row	11	**Comment:** Indications: one has to bear in mind that treatment options vary by region and time. Resistance rates against “less critical CIAs” may be or may become so high over time due to their “preferred use” that these ABs may lose their efficacy, and this may vary by region. Also note that in some MS, only a limited number of treatment options may have a MA or may be marketed, due to their limited market size and issues with languages on labels. Hence, it might be better that indications/pathogens for which all data requirements have been fulfilled should be mutually approved. The use should then be managed with appropriate language on the SPC. The latter may also not be static over time as resistance to first choice products increases, hence once more the need to have products available as alternatives and for which a full risk assessment for each indication has been performed. In this respect, lessons should be learned from human medicine. For example and additional to references submitted with the consultation,	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		another recent publication by Livermore's group: *<u>Abstract:</u>* ***Objectives*** *We examined the 4 year trend in antimicrobial susceptibilities and prescribing across levels of care at two London teaching hospitals and their multisite renal unit, and for the surrounding community.* ***Methods*** *Laboratory and pharmacy information management systems were interrogated, with antimicrobial use and susceptibilities analysed between hospitals, within hospitals and over time.* ***Results*** *A total of 108717 isolates from 71687 patients were identified, with significant differences (at P < 0.05) in antimicrobial susceptibility between and within hospitals. Across the 4 years, rates of ESBL-/AmpC-producing Enterobacteriaceae ranged from 6.4% to 10.7% among community isolates, 17.8% to 26.9% at ward level and 25.2% to 52.5% in critical care. Significant variations were also demonstrated in glycopeptide-resistant enterococci (ward level 6.2%–17.4%; critical care 21.9%–56.3%), MRSA (ward level 18.5%–38.2%; critical care 12.5%–47.9%) and carbapenem-resistant Pseudomonas spp. (ward level 8.3%–16.9%; critical care 19.9%–53.7%). Few instances of persistently higher resistance were seen between the hospitals in equivalent cohorts, despite persistently higher antimicrobial use in Hospital 1 than Hospital 2. We found significant fluctuations in non-susceptibility year on year across the cohorts, but with few persistent trends.* ***Conclusions*** *The marked heterogeneity of antimicrobial susceptibilities between hospitals, within hospitals and over time demands detailed, standardized surveillance and appropriate benchmarking to identify possible*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		drivers and effective interventions. Homogeneous antimicrobial policies are unlikely to continue to be suitable as individual hospitals join hospital networks, and policies should be tailored to local resistance rates, at least at the hospital level, and possibly with finer resolution, particularly for critical care. Luke S. P. Moore Rachel Freeman, Mark J. Gilchrist, David Livermore et al., 2014. Homogeneity of antimicrobial policy, yet heterogeneity of antimicrobial resistance: antimicrobial non-susceptibility among 108717 clinical isolates from primary, secondary and tertiary care patients in London J. Antimicrob. Chemother. (2014). doi: 10.1093/jac/dku307 Open Access, published August 12, 2014 Note that in some MS, there is a tendency to develop formularies based on active ingredient, irrespective of approved indications, and where off-label use is promoted and in some cases in preference to an authorised medicine with the appropriate indication. Such practices render the MA procedures including referrals superfluous and bypass any proper risk assessment and management process.	
Table 6, administration	11	**Comment:** Note that in human medicine and especially in general practice, a 50 kg person receives the same oral dose of an antibiotic as a 100 kg person. This is also not accurate dosing.	Due to the condition of which animals are medicated in groups it is not possible to extrapolate from the human situation.
Table 6, restrictions on cascade	11	**Comment:** This makes sense, but then unintended consequences from other risk management measures driving cascade use must be avoided.	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
use			
1507	11	**Comment:** Recently generic versions of cefquinome are becoming available on the market. **Proposed change:** please add: 4th generation cephalosporins (cefquinome)".	Agreed.
1561	11	**Comment:** The reference needs to be inserted. **Proposed Change:** antimicrobial consumption (~~REF to reflection paper on collecting data per animal species~~ **EMA/ESVAC, 2012**), the	The reference has been inserted.
1602-1603	11	**Comment:** Please note that oral administration neither equals growth promotion nor prevention. Therapeutic doses are administered for prevention claims, whereas label doses for growth promotion (approved in the past), were (significantly) lower than the label dose for a prevention or a treatment claim. For certain diseases in swine but particularly in poultry, oral administration may be the only option (also sometimes depending on intrinsic properties of the antibiotic which may be toxic when administered parenterally).	See above.
1614-1615	11	**Comment:** It is unclear what "sales" means. The addition of special AB classes when it is a program for all antibiotics appears somewhat as a contradiction. The possibility of a comparison of all different classes is very important in an impact analysis. **Proposed change: "**Monitoring by ESVAC of changes in ~~sales~~ **use volume** for all antimicrobials ~~in particular fluoroquinolones and cephalosporins~~ as a means to measure impact of actions implemented."	See above. New text: *"Monitoring by ESVAC of changes in antimicrobial consumption in particular fluoroquinolones and cephalosporins as a means to measure impact of actions implemented."*
1620-1621	11	**Comment:** Such an analysis should include animal target pathogens (as stipulated in the new Animal Health Law) as well as zoonotic pathogens and	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		commensals to provide a complete picture and analyse trends for all three categories.	
1648-1715	11	**Comment:** Annex 2 should mention that many VMPs containing antimicrobials have been registered using other routes than the Centralised Procedure.	New text: *"It should be noted that other AMs have been authorised using other routes than the Centralised Procedure."*
1827-2222	11	**Comment:** In Annex 5, it would be helpful to sort the references into either alphabetical or quoting order.	Corrected.
165	13	**Comment**: It is suggested that the pleuromutilins are included alongside the macrolides **Proposed change**: Category 1. Certain penicillins, macrolides, pleuromutilins, tetracyclines and polymyxins belong to this category.	Please note that the question from the Commission concerned compounds and classes listed as CIAs by WHO. Pleuromutilins is not listed and thus out of scope for this task.
326	13	**Comment**: Pleuromutilins (tiamulin and valnemulin) should be included in Table 1, in Category 1. **Proposed change**: Include pleuromutilins in Table 1 Category 1. Under Antimicrobial class - Pleuromutilins Under Zoonotic hazard – Campylobacter spp Under probability of resistance – Low Under Veterinary medicine – Approved (including group medicine) Under Concluding remarks – Compliance with responsible use principles is necessary to reduce risk.	Please note that the question from the Commission concerned compounds and classes listed as CIAs by WHO. Pleuromutilins is not listed and thus out of scope for this task.
202-203	13	**Comment**: 'treatment guidelines need to be locally created and implemented	Noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		rather than developed at EU level.' This conclusion is supported	
1429-1430	13	**Comment**: 'Despite the ban of antimicrobial growth promotion from 2006, the use of preventive antimicrobial courses still persists.' Currently, prevention claims are valid indications in the EU. Some growth promoters, which were not under veterinary prescription or control also had disease prevention effects. Approved products can be used legitimately for prevention and are done so by veterinarians who perceive a high risk if they are not included e.g. Strep suis as mentioned but also post-weaning diarrhoea associated with Escherichia coli if products like zinc oxide are not permitted. This has resulted in the extensive use of colistin in some countries. The EU has to decide whether preventive use is acceptable or not as an indication and do not confuse it with growth promotion. **Proposed change**: Delete 'Despite the ban of antimicrobial growth promotion from 2006,'	See above Agreed. Next text added: *"The use of antimicrobials for routine or systematic prevention of disease is of concern. There was a ban of antimicrobial growth promotion in 2006. However, systematic preventive use of antimicrobials is routinely practised in some intensively reared livestock."*
1450-1455	13	**Comment**: In addition to the cost of disease associated with Strep suis and estimated at €60 million, which is endorsed a similar mortality figure of 2% could be put on post-weaning mortality due to E. coli if left untreated with zinc oxide or colistin. A ban on prevention use could affect 95% of pig farms and a cost of €190 million could be estimated. This explains why vets and farmers require to be able to use antimicrobial substances at times of known high risk situations. **Proposed change**: Insert 'A similar mortality figure of 2% could be put on post-weaning mortality due to E. coli if left untreated with zinc oxide or colistin.	Agreed, text modified accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A ban on prevention use could affect 95% of pig farms and a cost of €190 million could be estimated.'	
1499	13	**Comment**: In Table 6. Possible regulatory risk management measures, under section SPC restrictions at reducing exposure to the antimicrobial there is consideration of 'No prophylactic use' and 'No metaphylactic use'. This is considered to have a detrimental effect on the health and welfare of animals under the care of the veterinarian. Currently, a definition of prevention and metaphylaxis has not been given by the EMA and the Guideline is still under consideration. It is considered dangerous to propose such changes before they are defined. This could have an effect on a number of products that have the legitimate indication of prevention. It is not thought that any products has a specific metaphylactic claim as such in the EU. **Proposed change**: It might be better to remove Prophylactic use and Metaphylaxis from the table.	See above.
1499	13	**Comment**: In Table 6. It also discusses the possibility of restrictions from use as mass treatment for herds and groups of animals. Treatment of individual animals only. This is impractical especially when you may be dealing with thousands of animals. Very few farms would have the manpower or money to treat and handle whole herds of pigs by injection, especially as they grow beyond the weaner stage up to 100kg. **Proposed change**: It might be better to delete Herd/flock and group treatments.	Not agreed. The table addresses a broad range of possible risk management measures for different species. The text has been modified to make clear that those are possible options. New heading: *"Possible options for regulatory risk management"*

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1499	13	**Comment**: In Table 6. In Dosing regimens, administration it describes 'Restriction from use as formulations that prevent accurate dosing for individual animals e.g. in feed or water.' Again while dealing with large numbers of animals it is almost impossible to rely on injections only. It is impractical and costly and potentially hazardous to the administrator. It is not surprising therefore in the pig world, antibiotic administration in most countries is most commonly given in feed, on feed or via the drinking water. **Proposed change**: Remove 'Restriction from use as formulations that prevent accurate dosing for individual animals e.g. in feed or water.'	Not agreed. See comment above.
1570-1581	13	**Comment**: Beyond one Canadian study there is no direct evidence for potential beneficial effects to human health of these risk mitigation measures or that any of these proposed changes will have any direct effect on human antimicrobial resistance. It is surprising that the effects of voluntary or compulsory withdrawal of cephalosporins for use in food animals in several EU MSs have as yet not been assessed. Wouldn't this be a good thing to do to prove that these potential measures might have some impact?	We agree that the effects of the withdrawn of cephalosporins in some MSs should be investigated and published. We believe that this is currently been investigated in some countries.
1582-1583	13	**Comment**: 'Negative effects of the withdrawal of cephalosporins in slaughter pigs include reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaners with oedema disease.' This is incorrect it was thought to be due to the introduction of the Yellow card system in Denmark and restrictions of use of all antimicrobials. (Alban et al, 2013). **Proposed change**: 'Negative effects of the introduction of the Yellow card system in Denmark for pigs include reports of increases in the occurrence of	Response: Change made . New text: *"Reports of increases in the occurrence of enteritis and peritonitis in slaughter pigs and of weaners with oedema disease."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		enteritis and peritonitis in slaughter pigs and of weaners with oedema disease.'	
1602-1603	13	**Comment**: 'Despite the ban on growth promoters, many compounds are still given by the oral administration route for preventive purposes.' It is not despite the ban of growth promoters it is because of the ban of growth promoters that many therapeutic antibiotics are used for prevention. **Proposed change**: 'Because of the ban on growth promoters, many therapeutic compounds are given by the oral administration route for preventive purposes.'	The text has been amended to avoid confusion. *"The use of antimicrobials for routine or systematic prevention of disease is of concern. There was a ban of antimicrobial growth promotion in 2006. However, systematic preventive use of antimicrobials is routinely practised in some intensively reared livestock."*
References	13	Alban, L., Dahl, J., Andreasen, M., Petersen, J.V. and Sandberg, M. (2013) Possible impact of the 'yellow card' antimicrobial scheme on meat inspection lesions in Danish finisher pigs. Preventive Veterinary Medicine, 108, 334-341 DANMAP 2006 (2007) Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. Section: Antimicrobial consumption in animals, pp 17-22.	References have been added.