18 July 2011
EMA/CVMP/257610/2011
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on the 'CVMP strategy on antimicrobials 2011-2015' (EMA/CVMP/287420/2010)

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

Stakeholder no.	Name of organisation or individual
1	Dutch Federation of Agriculture and Horticulture
2	Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail - Agence Nationale du Médicament Vétérinaire (ANSES-ANMV)
3	COPA-COGECA
4	Federation of Veterinarians of Europe (FVE)
5	Association of Poultry Processors and Poultry Trade in the EU (AVEC)
6	IFAH-Europe
7	Veterinary Medicines Directorate (VMD)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The Dutch Federation of Agriculture and Horticulture would like to support your document (CVMP strategy on antimicrobials 2011-2015). We would like to pay special attention to: - Stimulating of developing small spectrum products - The use of fluoroquinolones and 3e and 4e generation cephalosporins because of their use in the human sector. - An equal way of monitoring the use of antimicrobials in the EU member states	The comments are very much appreciated.
2	The ANSES- ANMV welcomes the CVMP strategy and thanks the CVMP for this accomplished paper. The CVMP strategy on antimicrobials is supported, especially on the following points : Responsabilities should be shared by Authorities, Companies and prescribers. • Need for availability for minor species • Need for restriction of off-label use for identified critical antimicrobials • Need for review of the efficacy guidelines on antimicrobials: *Specific requirements should be defined for the critical antimicrobials.* *It is no longer acceptable to recommend the use as a second line antibiotic, while demonstration of efficacy of such critical antimicrobials is currently only accepted on the basis of non-inferiority trial with first line antimicrobials…* • Need for an update of the SPCs of antimicrobials :	The comments are very much appreciated. With regard to the three points for discussion we fully share your concern although these points are not detailed in the strategy. The need for a guideline on pack sizes will be considered.

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	The update of the SPC is needed for old antibiotics (dosages and long treatment duration) as well as for more recent ones : We notice the multiplication of dosages for the same indication (fluoroquinolones, florfenicol, etc…). This is a very complex situation, which becomes more complex with generics, but which is not satisfactory at all. The possibility to have several dosages is not called into question, but this should be adapted to scientific knowledge and/or to differentiate the claims. However, the ANSES-ANMV is of the opinion that many of these objectives can only be reached if there is in parallel an improvement of the regulation, especially on : • Global Marketing Authorisation and duration of data protection. All efforts for availability could be useless if these problems are not solved. • The possibility to restrict the off-label use of critical antimicrobials as well as the possibility to have specific requirements for these antimicrobials also request improvement of the regulation. • The current marketing authorisation legislation allows for the benefit-risk assessment of a given product to be considered on its own merit only. However, there is need for an extended benefit-risk assessment which fits with the global vision. Provision should be made to develop a specific benefit-risk assessment to include critical factors (such as relevance of the claim, existence of other products, withdrawal periods which are economically attractive, etc…) The ANSES-ANMV also considers that some other issues need to be	

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	discussed, and would like to make the following proposals to CVMP : 1. The pack sizes: differences in herd sizes and husbandry practices are acknowledged among Europe. However, there is a tendency for the MAH to increase the size of packaging as well as the size of the vials of injectable products. Sometimes, the volume which would be needed to treat only one sick animal, after a prompt diagnosis by the vet, and prudent usage of the product, does not exist on the market. This is also an encouragement to off label use. A reflection paper or a guideline would be welcomed. 2. The different usages in field: the possibility to promote consensus building of the use of products depending on pathologies should be discussed. The prescribers would also beneficiate to have clear information on which practices lead to selection, and which practices can minimize the risk of antibioresistance. This also implies to precise the definition of “prevention at herd level” which is not understood in the same way by authorities (diagnosis of a disease is needed) and by prescribers (presence of germs). 3. The impact of environmental spreading of resistant bacteria after treatment at flock level would require more attention in future.	
3	European farmers and their agri-cooperatives have always recognised the growing concern amongst consumers over the treatment of animals with antimicrobials. It is in the farmers’ interest to ensure a sustainable animal production with healthy and productive animals. **Improving animal health** is one of the best ways to reduce the need for antibiotic treatment in animals. Livestock farmers and breeders can contribute by offering good	Thank you for providing these highly relevant comments. We note that we share a common view on the topic.

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	hygiene, proper feed, appropriate husbandry and good management practices as opposed to general use of antibacterials. However, despite such efforts, animals can still get sick and they need to be treated. Improving antimicrobial use requires **transparency** and **responsibility** of all key actors: farmers, veterinarians, veterinary pharmaceutical industry, distributors of veterinary medicines and competent authorities. Prudent use of antimicrobial agents in animal production aims at: - Ensuring bacterial infections in animals and humans can continue to be treated in future; - Preventing the transmission of resistant bacteria from animals to humans through the food production chain or from animals to humans directly; - Avoiding the spread of resistant genes in the environment; **Copa-Cogeca would like to stress the importance of:** **1. VETERINARY PRESCRIPTIONS AND APPROPRIATE AND EFFECTIVE DIAGNOSTIC TOOLS** It is important to ensure that: - the **use** of antimicrobial agents is **strictly based on veterinary prescriptions**; - any antimicrobial prescription is provided by either **a vet responsible for the treatment of a particular animal** or by **the vet in charge of following-up the specific production purpose** of the herd (for instance bovine milk production or fattening pig production);	

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	- the use of antimicrobial agents is in accordance with the provisions of the prescription; - the treatment is recorded in order to evaluate its results, and for possible adjustment of the treatment protocol; - better monitoring of the companies involved in the placing on the market of antimicrobials. It is important to ensure that a continued availability of **specialised veterinarians** can be found, who are able to provide a prompt and appropriate prescription. Experience has shown that many EU Member States are short of veterinarians specialised in farm animals, who, geographically speaking, may often be located a considerable distance away from the farm in question. Moreover, it is important to train farmers either directly or indirectly through farmers' organisations, with particular focus on improving the knowledge of all farmers on the responsible use of antimicrobials and preventative measures for new emerging diseases. **2. MONITORING THE USE OF ANTIMICROBIALS AND SURVEILLANCE PROGRAMMES ON ANTIMICROBIALS RESISTANCE** Given that **some EU countries have NOT put in place a monitoring and surveillance programme**, Copa-Cogeca believes it is necessary to encourage every EU country to do so. It is particularly important that monitoring programmes are developed in line with national surveillance programmes, by involving control authorities, farmers organisations and the pharmaceutical industry in their development. This would help to reduce additional costs at farm level and prevent abusive use of products. It is hugely important to have a harmonised system for collecting data	

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	from all EU Member States, given that this constitutes the first step of an accurate risk assessment on the use of antimicrobials. Regular reports would enable a better understanding of antimicrobial resistance and trends over a long period of time. There is a lack of information relating to the amount and types of antimicrobials used by farmers and the prescriptions provided by veterinarians. At the moment information is only available at sector or MS level. More information should be made available about average use per sector, and the percentage of farmers using over the average and the reasons for this. As well as allowing an understanding of the reasons why some livestock farmers are successful in reducing antimicrobial use, more transparency would also help livestock farmers to benchmark themselves against one another. **3. INVOLVING ALL ACTORS CONCERNED** Improving antimicrobial use requires the involvement of **all key players.** - For the **veterinary pharmaceutical industry**: to exclusively approach authorised professionals and not livestock producers directly, to have a clearer price policy for antimicrobial agents (discount practices when issuing larger quantities is an issue). - For **distributors**: to deliver antimicrobials solely upon proof of prescription. A log book may help to monitor sales and purchases of such products. It would help to control the sale of non-prescription drugs and their use by distributors, as well as ensuring that they are authorised to distribute animal health products. - For **veterinarians**: to adjust their prescriptions, to focus more and more on their activities with respect to prevention and other	

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	associated management skills. - For **farmers**: to respect prescriptions, to record use of drugs, to increasingly consider disease prevention in their activities. - **Imports of meat from third countries**: systematic monitoring is needed on imports of meat and animal products from third countries to ensure that EU maximum residue limits for veterinary drugs are respected. **4. GUIDELINES FOR THE RESPONSIBLE USE OF ANTIMICROBIALS** Guidelines and decisions regarding the use and introduction of restrictions should be based on sound scientific risk assessment. We fully support the development of voluntary programmes which promote the responsible use of antimicrobials. Copa-Cogeca is currently involved in the European Platform for the Responsible Use of Medicines in Animals (EPRUMA). Farmers have the possibility of gaining access to a comprehensive and practical framework of best practices for the use of antimicrobials in the farming sector, contributing to the development of successful management programmes for the entire farm. **5. RESEARCH AND DEVELOPMENT ACTIVITIES** **Reinforce the development of new, innovative antimicrobial medicines** – It is important to ensure new and innovative products for the market which cover all species, including minor species and minor uses for which there is often a lack of interest from private industry. This would, at the same time, address some of the problems relating to the inappropriate use (off-label) of antimicrobial agents, which in certain circumstances is the only way of controlling an	

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	infectious disease. **Improving diagnostic tools** – assess the possibility of replacing or strengthening existing diagnostic, treatment and prevention measures should be further explored. The farming community often faces ineffective measures due to well-established, multi-resistant pathogens. **Action to improve animal health** - improving animal health is one of the best ways to reduce the need for antibiotic treatment in animals. More coordination on certain key applied research projects in the framework of animal health and production systems is necessary to gain a better understanding of good practices with a positive impact on the farming community's competitiveness and make it less dependent on the use of antimicrobial agents. **6. THE NEED FOR GLOBAL ACTION** Promoting information-sharing between interested parties is essential. With a view to controlling the use of antimicrobial agents, **global action is absolutely essential**. Here, global is meant **in geographical terms**. It would be deceptive and dangerous to continually implement regulations in developed countries without first enforcing those which already exist and to apply basic, fundamental rules in third countries.	
4	Maintaining the efficacy of antimicrobials is a fundamental « One Health » issue contributing to the Public Good. It requires the involvement and commitment of all the parties involved, from pharmaceutical companies to the end users like farmers, pet owners and citizens, from breeders to farmers, from veterinarians to medical doctors, without forgetting the food industry. Addressing responsibility to everyone involved must be one of the primary considerations in the future strategy. Veterinarians are qualified professionals who can	Thank you for providing these highly relevant comments. We note that we share a common view on the topic.

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	provide their scientific knowledge for supporting and leading the campaign. FVE wishes to collaborate with all stakeholders involved for the development of an effective common approach. The mission of the Veterinary Profession – represented by the Federation of Veterinarians of Europe (FVE) - is the protection of Animal Health, Public Health and Animal Welfare. One of the most important tasks of the profession is the prevention and control of animal diseases; in particular the prevention of zoonosis and food borne disorders, which is crucial for assuring public health. Further to more fundamental measures - like zootechnics, good animal husbandry practices and responsible animal ownership - veterinary medicinal products are fundamental in the treatment and prevention of animal diseases. However, with regard to the use of antimicrobial agents this is not without consequences. Exposure of bacteria to antimicrobials can lead to selective pressure and the selection of bacteria that are less susceptible or even resistant to treatment. The exchange of resistance-factors between bacteria, and the transmission of resistant bacteria between different (animal-) species, including mankind, further increase the risk. The Federation of Veterinarians of Europe is well aware of the occurrence of antimicrobial resistance in bacteria and is concerned by the current increase and its cross-species transmissibility. FVE and its members take all the necessary measures to tackle these trends in food–producing animals, as well as in horses and in companion animals. The veterinary profession, organised in FVE, proposes that the following recommendations must be taken into account in the future CVMP Strategy on antimicrobials concept: - Responsibility should be addressed to all the involved parties;	

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	veterinarians, farmers and animal keepers, industry and society - Measures to be taken are science based, realistic, mandatory, proportionate and sustainable. The approaches in the veterinary field and in the human medical field should be well coordinated. - Preventive use of antimicrobials must be minimised. They may not be used to mask poor farm management or inadequate zootechnics. Biosecurity, hygiene-standards, animal husbandry practices and vaccination programmes must be developed and improved where necessary. - The implementation of best practices in animal husbandry and of preventive programs under the guidance of their veterinarians should be promoted amongst farmers and animal keepers. Farm visitation systems should be in place and be based on a 'One to One' relationship between farmers and veterinarians. Veterinarians will have a limited amount of animals under their care, will make reports with their recommendations for the farm in question and will follow-up how the recommended measures are implemented - The development of diagnostic – if possible 'on site' - tools in order to differentiate viral infections from bacterial infections in the field. - The restricted use of some critically important antimicrobials and novel products (e.g. only for second intention and/or after justification) in order to preserve the therapeutic arsenal for human beings. However, it should be taken into consideration that prohibition of their use in animals, even for cases that are necessary for, will hamper not only animal health, but human health and animal welfare as well. Human health and Animal health is a 'One health' issue. - Introduction of a system which will reduce the need for off-label use of antimicrobials under "the cascade", by increasing the availability of	

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	veterinary medicinal products in all countries. - In order to be able to take effective measures in the veterinary field, there is need for a clear and unambiguous assessment of the use of antibiotics including those in medicated feed, by species and by region. This should be complemented by monitoring the use at farm level, and be linked with the monitoring of the development of antimicrobial resistance. Therefore, FVE specifically welcomes - amongst several other important actions being taken - the initiative on the “European Survey on Veterinary Antimicrobial Consumption”. - Training of veterinary students and veterinarians focusing on antimicrobials and their responsible use must be intensified and supported, while actions keeping veterinarians’ awareness as acute as possible should be developed. - Advertisement of medicinal products to non-veterinarians (farmers and public) will be prohibited. We believe that advertisement of veterinary medicines to people without any scientific background and therefore unable to evaluate the benefits and the risks of the use of a medicine or antimicrobial in an animal, is one of the main reasons that has led to the excessive use of antimicrobials. - European Commission and the Member State authorities should take the necessary measures to support the animal health sector in a similar manner to that on the human side and to provide training and education support in the implementation of responsible use of antimicrobials in veterinary medicines across the Community. FVE considers education a crucial part of the strategy to be set up, and must apply to a broad range of people. The public in general must be aware of the risks associated with the use of antimicrobials without any professional advice or prescription, and especially when purchased via the Internet. Communication campaigns like the European	

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	Antimicrobial awareness day and the French « antibiotics are not automatic » initiative must inform the public at large. Contrary to what has been the case previously, these campaigns must embrace the animal health sector in equal measure. The veterinary profession is and wishes to remain part of the solution of the AMR. Veterinarians through the FVE wish to contribute actively and responsibly to strive forces with all stakeholders and the Commission to fight AMR.	
5	We welcome the strategy paper from EMA. Several concerns highlighted by stakeholder have been taken account (DG SANCO consultation Jan-Mar 2010). We also welcome that EMA will collect data on the use of antimicrobials in animals and make sure that the approach is harmonised. We have however, concerns that a harmonised approach to the monitoring of the antimicrobial resistance in animals at the EU level and the objectiveness of the data collected can be very difficult for the following reasons: - Member States have different structures for the supply of veterinary medicines, i.e. is there a separation of the prescription (veterinarian) and the supply of the medicines (veterinarian/ pharmacy) or are the functions integrated? - Is the prescription of veterinary medicines done by an official veterinarian, an independent veterinary practitioner and or the company veterinarian and could there be conflicts of interest in the prescription and amounts prescribed? Is there a need for a second	Thank you for providing these highly relevant questions which have been forwarded to the ESVAC program for consideration.

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	opinion before medicines are administered? - If the farmer administers the medicines does he closely follow the instructions for correct use and is this checked by the prescribing veterinarian? - Which data should be collected and where? (breeder level, broiler farm, layer farm, veterinary medicines used, batch numbers, how much is effectively used and how much is wasted, how much have been taken by the animals? - Is the level of education of veterinarians, famers and other staff involved in the animal for food production chain harmonised at EU level in terms of knowledge to veterinary medicines and administration of medicines and is the legislation applied and enforced in a similar way? - Is the price policy of the pharmaceuticals objective and not encouraging excessive use at discount prices – and does it differ from one Member State to another? - How is the use monitored for food animals imported from third countries for EU consumption	
6	IFAH-Europe thanks CVMP for the opportunity to comment on the "CVMP Strategy on antimicrobials 2011-2015". When compared to the strategy 2006-2010, The CVMP Strategy 2011-2015 document takes quite an active approach in terms of amending current product authorisations, restricting new antimicrobial innovation and promoting its vision of prudent use (we would prefer the use of the term 'responsible use' as this is part of the EPRUMA name) by means of SPC usage instructions. It is suggested that conflict exists between the stated *large gaps in indications* and *encouragement of initiatives to increase the number of product*	Thank you for these comments. CVMP shares your concern regarding lack of innovation in this field. However, we find that the need to maintain the efficacy of the existing antimicrobial products is more urgent. We understand that predictability is very important for Industry and this has been taken into consideration when drafting the Strategy.

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	alternatives on the one hand, versus the limitations for new anti-infectives proposed on the other hand: *narrow spectrum only, restriction as last resort medicines for humans, prudent use for pivotal clinical trials*. The restrictions in use effectively place antimicrobials in the "minor use" category, while simultaneously the cost of developing a new antimicrobial has increased markedly. This stark in-balance is a major disincentive to invest in this area. IFAH-Europe believes that two consequences will follow. First, re-shaping "allowable" antibiotic classes by means of the Strategy would unnecessarily reduce the range of available products and would likely result in the use of older antibiotic classes for which co- and cross-resistance is not excluded. Second, without evidence upon which to make some of the Strategy recommendations for specific product uses, the administrative guidance may put products, animals and food safety at greater risk than if no intervention were made. The Strategy would benefit from success metrics. These would help the CVMP to identify which interventions are or are not effective and to what extent. Without a means to assess the outcome of the Strategy, including all of its components, there is no means to improve or change it in the future. While the retrospective list of accomplishments for the prior Strategy papers are provided in the Annex, there is no evidence provided to show that the efforts have actually reduced food borne disease, including AMR pathogens. With regard to these various points, IFAH-Europe would like to propose a workshop between stakeholders as a means of generating greater clarity and understanding for all parties concerned.	
7	The VMD welcomes the updated CVMP Strategy on Antimicrobials and	Thank you for these comments. We acknowledge the need for collaboration and communication. CVMP's main

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	overall supports the proposed actions. The VMD, in its capacity as a NCA but also in its capacity as the Chair of the HMAv Taskforce on Antimicrobial Issues, would like to emphasise the point that is already made in the CVMP strategy, which is that in order to effectively deliver the different elements of the CVMP strategy good collaboration with many other organisations is essential. In particular, the HMA and hence the network of regulatory agencies have an essential role to play and it is important that the CVMP and HMA Strategies on antimicrobial issues are aligned. A further point VMD would like to emphasise is that better collaboration with industry would help to improve understanding on both sides and could help overcome the barriers to innovation and encourage surveillance programmes that could be used to update aspects of products dossiers/MAs. One element that does not seem to be clearly highlighted in the CVMP strategy concerns communication. It is noted that there are some elements relating to communication in some of the areas identified, however we consider that it would be beneficial to include a section in the strategy dedicated to communication. A further element that we believe should be highlighted is the CVMP's important role in influencing new legislative proposals from the Commission. For example, the development of new antimicrobials for use in animals may warrant additional data protection, as perhaps should the development of new convenient formulations for existing antimicrobials which remain effective. Another example will include ensuring that any legislative proposals to restrict the use of certain antimicrobials are evidence based and practical. Another example would be in the area of the extent to which benefit:risk assessments can take into account wider factors such as whether a short	communication tools are the approved SPC and EPARs together with our guidance documents and interested parties meetings. CVMP follows closely the development of the discussion at HMA and welcome the cooperation. The CVMP has communicated its view on the intended revision of legislation in *the CVMP analysis of the functioning of current veterinary legislation and proposals for its evolution and comments on the Commission paper* (EMA/CVMP/463298/2010 from July 2010). Our view on benefit/risk assessment is presented in our *Recommendations on the evaluation of the benefit-risk balance of veterinary medicinal products* (EMEA/CVMP/248499/2007 from April 2009). At present we have no intention to add economical aspects to the benefit/risk evaluation as proposed by VMD.

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	withdrawal period might lead to a product being favoured on economic grounds but which may not be the most suitable choice in terms of responsible use of antimicrobials.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 18-22	4	Comments: **Promotion of responsible use of antimicrobials should be done through an holistic approach which includes all species** Proposed change (if any): Work in collaboration with other interested parties to promote prudent and responsible use of antimicrobials throughout EU in food producing animals, as well as in companion animals. Approvals of antimicrobials are based on the assumption that they will be used responsibly and according to the label and veterinary prescription and thus for the risk mitigation measures to be effective, it is important that the recommendation given in veterinary medicine literature are fully implemented in everyday veterinary practice.	Our Strategy comprises food producing and companion animals. We regret the inappropriate use of the expression "from farm to fork". The text is amended according to the proposal. Prudent" and "responsible" have the same meaning in this context. The expression "prudent use" was used consequently throughout the document. However, as the two are synonyms have now changed the wording. "Product literature" refers to the SPC and package leaflet which is the information linked to the product which CVMP authorises. We did not intend to cover all different kinds of literature in the veterinary field.
/Line 28	4	Proposed change (if any): of medicinal products in animals when appropriate	Veterinary medicinal product is a comprehensively used standard phrase.
Line 38	4	Comment: **The responsible use of veterinary medicines is a part of Good Veterinary Practice.** **Veterinary medicinal products should only be used after careful examination of the animals and the conditions under which these are kept. Non pharmacological interventions, for example improving housing conditions, etc. should always be considered before and preferred above**	See comment on "prudent" above.

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		pharmaceutical interventions. **Where possible the clinical diagnosis should be supported by susceptibility testing.** **Results of a treatment should be evaluated and taken into account in future treatments.** Proposed change (if any): in a responsible way to avoid unnecessary selection pressure for AMR.	
Line 39	4	Proposed change (if any): Pivotal clinical trials should be conducted according to responsible use principles.	See comment on “prudent” above.
Line 44	4	Comment: **add the following sentence** Proposed change (if any): CVMP should address responsibility to all the involved parties; veterinarians, farmers and animal keepers, industry and society.	The bullets are similar to the headings of each section. This structure of the document should be kept without additions.
Lines 109-112	4	Proposed change (if any): CVMP would like to encourage initiatives to increase availability of all approved veterinary medicines covering different species and indications including those with a limited market to all European countries.	The proposal is not supported. We want to cover both the need for new products and the need to market approved products in all countries (if appropriate and provided AMR is not an issue).
Lines 122-128	4	Comment: **Adoption of this position could lead to hampering**	The comment is partly agreed with. We do see a conflict as “strict and clear rules” and “safeguard public health” might in

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		of the innovation for veterinary field. However, novel products for animal treatment, which enable veterinarians to efficiently respond to emerging risks and in that way safeguard also public health, are necessary. What is evident is that strict and clear rules governing the use of these products have to be laid down. Moreover, innovation of diagnostic tools for veterinary use has to be encouraged, in order to assist the diagnosis and therefore proper treatment of animals. Proposed change (if any): "… CVMP recognises the need for novel products for veterinary use, as it happens for humans. However, it realises that these ones have to be used according to strict and clear rules, in order to safeguard their efficacy to humans and animals. CVMP intends to collaborate closely with the human and veterinary side and communicate with industry at an early stage to allow specific assessment of such drugs and prepare clear rules for their use. Such rules should be made based on risk assessment in each case to allow appropriate decisions without unnecessarily restricting availability on the veterinary side. Moreover, there is a clear need for enforcement of the development of diagnostic tools, in order to assist diagnosis and therefore proper decisions for treatment of animals.	some cases imply a restriction of use for the veterinary side. We do recognise the need for new products, however, on the human side there are identified therapeutic gaps which cannot be filled with existing molecules/classes of antimicrobials and to our knowledge such an urgent need has not been identified in veterinary medicine. We agree that diagnostic tools are important in this context. A sentence has been added to the revised strategy.
Line 142	4	Proposed change (if any):	See comment on "prudent" above.

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		responsible use principles the SPC should	
Line 149-151	4	Comment: **Development of proper diagnostic tools can also help to easily identify infected individuals at early stages and therefore help avoiding group treatment. Therefore, more sustainable practices can be used instead of it.** Proposed change (if any):	Agreed. A sentence is added.
Line 161	4	Proposed change (if any): …according to responsible use principles.	See comment on “prudent” above.
Line 192	4	Proposed change (if any): …should consider responsible use principles	See comment on “prudent” above.
Lines 194-195		Proposed change (if any): To allow products to be used in a responsible way in practice it is crucial that such studies are designed in a way that takes into account responsible use principles.	See comment on “prudent” above.
Lines 218-221	4	Comment: **A more holistic approach should be adopted. Much attention should be paid, in order to ensure that unnecessary restrictions applied for veterinary field would not lead to unsuccessful handling of emergency situations, including zoonotic diseases, and loss of control both in human and veterinary side.** **Add the following sentence.** Proposed change (if any): It should be taken into	In principle the proposal is supported. However, this is stated already elsewhere in the document eg. line 126-128.

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		consideration that prohibition of their use in animals, even for cases that are necessary for, will hamper not only animal health, but human health and animal welfare as well. Human health and Animal health is a 'One health' issue.	
Line 238	4	Proposed change (if any): …to ensure responsible decisions.	See comment on "prudent" above.
Line 244	4	Comment: **Enforcement of pharmacovigilance systems is an important and critical point that should be included in the future strategy concept.** Proposed change (if any): …of a product authorised for veterinary use from the label recommendation. Pharmacovigilance systems should be enforced, in order to be able to identify cases of lack of efficacy the sooner and respond to them accordingly. Further work is needed to…	The proposal is not supported. This section concerns off-label use. It would not be possible or practical to include off label use in the pharmacovigilance system. Such use should be exceptional and be the responsibility of each veterinarian.
Lines 250-254	4	Comment: **Cascade is not optimal but cannot be missed. We do believe that the order of the cascade should be changed as follows: 1. a veterinary medicinal product authorised in one of the Member States under this Directive or under Regulation (EC) No 726/2004 for use with same animal species, or for the same indication; 2. a veterinary medicinal product authorised in one of the Member States under this Directive or under Regulation (EC) No 726/2004 for use with another animal species, or for the another**	The proposal for change gives the text a new meaning. The intension is to state that we see a need to allow an AMR risk analysis to be considered in relation to the cascade. We acknowledge the need to increase the availability of e.g. penicillin in modern dosage forms on the market to reduce off label use of broader spectrum antimicrobials. However, this message is given elsewhere in the document.

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		indication; 3. a medicinal product authorized for human use in the Member State concerned in accordance with Directive 2001/83 of the European parliament and of the Council under Regulation (EC) No 726/20004, or 3. a veterinary medicinal product prepared extemporaneously by a person authorized to do so under national legislation in accordance with the terms of a veterinary prescription. Moreover, uniformity in labels could reduce the use of the cascade. Proposed change (if any): For the future it would be appropriate to have a system which will reduce the need for use of "the cascade", by increasing the availability of veterinary medicinal products in all countries. In case of risks related to AMR special provisions should be foreseen, in regard to the use of "the cascade", that will allow proportionate risk mitigation following appropriate scientific risk analysis. CVMP will work with the European Commission and other stakeholders to see how they can reduce the need for off-label use without inappropriately comprising the clinical freedom of veterinarians, hampering in that way animal health and welfare as well as public health.	
Line 257	4	Proposed change (if any): of AMR related risks from antimicrobials for veterinary use and will contribute to any action…	The proposal is not supported. We intended to cover off label use of human medicinal products as well.
Lines 283-286	4	Proposed change (if any): In CVMP's view a global (EU)-strategy on antimicrobial resistance is urgently	Agreed. The sentence is amended. However, we don't see the need to specifically mention industry in this context.

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		needed. The management of this problem for society cannot be left only to the prescribing veterinarian, who is faced with sick animals; it can also not be left on the shoulders of the farmer, who has to obtain a benefit from the animal production and to animal keepers in general, as well as to the Industry.	
Lines 289-295	4	Comment: **Farm Visitation systems should be implemented and be properly controlled by the authorities. This will allow the enforcement of promotion of sustainable practices, which can lead to reduction of the antimicrobials needs; "prescription of biosecurity measures, etc" instead of prescription of antibiotics.** Proposed change (if any): Animal management/husbandry aspects should be included in the discussion as ultimately antimicrobials are not needed when the animals are healthy. The establishment of a farm visitation system should be considered which has to be based on a 'One to One' relationship between farmers and veterinarians. Veterinarians will have a limited amount of animals under their care. They will make reports with their recommendations for the farm in question - for example better herd management, availability of reliable, fast and affordable diagnostic tools for animal diseases, improved biosecurity measures, better feeding strategies, breeding for disease-resistance - and follow it up. Individual animal surveillance and treatment using modern electronic techniques are	Agreed. However, we feel that the level of detail would be too high with this amendment as farm visitations would not be within CVMP's remit.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		important points to consider. Use of vaccines should be promoted.	
Lines 299-304	4	Comment: **FVE strongly agrees with prohibition of advertisement of medicinal products to non-veterinarians (farmers and public). We believe that advertisement of veterinary medicines to people without any scientific background and therefore unable to evaluate the benefits and the risks of the use of a medicine or antimicrobial, is one of the main reasons that has led to the excessive use of antimicrobials and the development of antimicrobial resistance.** **Add the following sentence** Proposed change (if any): Therefore, prohibition of advertising medicinal products, particularly antimicrobials, to persons without scientific qualification should be part of the general strategic plan.	Agreed. However, we prefer to leave this conclusion for the European Commission to consider as such a general strategic plan is outside the CVMP scope.
157 to 164 Fluoroquinolones and 3rd to 4th generation Cephalosporins should not be used for general prophylaxis	5	Comment: Risk assessment of animal diseases should not be discriminated to concern only intensive farming. Small agricultural holdings, wild animals and pets and the health of humans contribute as much to the AMR in the environment. It is likely that much of the antibiotic resistance is a result of human influence/acting on both animal and human health. Furthermore the concerns stated under the chapter on monitoring are relevant here including the remark as how to monitor and assess the risk of antimicrobials used in third countries	CVMP's intension is to keep within our own remit which does not include use of antimicrobials in humans. Within veterinary medicine we believe the highest AMR related risk is linked to intensive farming.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
in pigs and poultry		exporting meat to the EU. Proposed change (if any): It is relevant to evaluate the use of human medicines and what is prescribed by doctors for cure of human diseases since this will add to the risk of AMR.	
232 – 254 Off label use	5	The veterinarian may need the off label use in emergency cases. There is a need to consider restrictions on use of specific antibiotics. It is paramount that any restriction is based on scientific evidence keeping in mind the reduced animal health and welfare that the restrictions may cause.	The CVMP agrees with the comment made.
18-22 (also 296-298)	6	Comment: The importance of responsible use is highly appreciated and aligned with EPRUMA, a European multi-stakeholder platform	The CVMP agrees with the comment made.
30 (also 39 and 137)	6	Comment: The OIE Terrestrial Animal health code 2010 Chapter is 6.10. It is important to specify what is meant by prudent use principles, because there are many documents available, each of which is slightly different. Proposed change: ..responsible use principles (i.e. OIE Terrestrial Animal Health Code 2010 Chapter is 6.10. Article 1) is applied…	See comment on “prudent” above.
34 (and 95)	6	Comment: The word “perceives” is not very strong. The bullet point and the title of Section 1 might be better with a more explicit statement of support. Proposed change: CVMP supports the availability of a range of effective antimicrobial treatments…	We find the expression sufficiently clear.

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35 (and 115)	6	Comment: The use of the word “encourage” does not provide sufficient explanation as to what CVMP will actually do to increase innovation. In Section 2, please include specific incentives to be provided for companies, such as expedited reviews, new regulations for novel products, support for improved data protection, etc. Proposed change: CVMP supports additional regulatory actions that can be implemented to support innovation.	Agreed, in principle However, exact measures that fit to all product types are difficult to include in a strategy document. Scientific advice for a particular product under development could provide the requested clarity.
39 (and 192)	6	Comment: It is important to specify the OIE Terrestrial Animal health code 2010 Chapter is 6.10. and the relevant chapter within, as well as which type of clinical trial. **Proposed change: As far as possible with the regulatory pivotal effectiveness trials, the OIE Terrestrial Animal Health Code 2010 Chapter is 6.10., should be followed.**	We have referred to OIE elsewhere and cannot see the need to detail the heading of this section.
41/42	6	Comment: This is in contradiction with the “large gaps in approved indications” (Line 101) and the future restrictions on labels of existing or new antimicrobials as interpreted from this vision statement, which reinforces this problem.	Agreed. However, innovation includes more modern formulations of “old” molecules, vaccines, better diagnostic tools etc. Even if AMR related risks have a heavy weight in the benefit/risk evaluation of new classes of antimicrobials and there might be a need to apply restrictions in such cases there is still a lot of room for innovation.
66	6	Comment**:** Selection pressure may be due to non-antibiotics, as for example, nutrient supply, resistance to substances such as copper, etc. Proposed change: …antimicrobials or by other	It’s unavoidable in case of antimicrobials and that is what is intended here.

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		mechanisms.	
91-94	6	Comment: This statement (re risk of MRSA in livestock spreading to humans) does not appear to take into account that two recent studies quantify the risk to human health from contact with livestock to be substantially lower than expected. Cleef BA, Graveland H, Haenen AP, van de Giessen AW, Heederik D, Wagenaar JA, Kluytmans JA. Persistence of livestock-associated MRSA after short term occupational exposure to pigs and veal calves J Clin Microbiol. 2011 Wassenberg MW, Bootsma MC, Troelstra A, Kluytmans JA, Bonten MJ. Transmissibility of livestock-associated methicillin-resistant Staphylococcus aureus (ST398) in Dutch hospitals Clin Microbiol Infect. 2011 Feb;17(2):316-9	No, these studies were not available when this strategy was published for consultation. However, neither of the two conclusions (that MRSA is frequently present after short-term occupational exposure, but in most cases colonisation is transient and that nosocomial transmission of ST398 MRSA is less likely than that of non-ST398 MRSA strains) warrants any changes to the text. There is indeed a risk of MRSA in livestock spreading to humans as discussed in these publications.
101/102	6	Comment: There is no specific strategy designed to increase minor species authorisation other than “encouragements” to industry. We would like - to ask CVMP to be more specific in this strategy, - that minor indications be also considered, - CVMP to keep this in mind during the indicated referrals on antimicrobial products (ref. 184-187), - to support significantly improved data protection for new antimicrobials to stimulate innovation.	We cannot be more specific but we do consider minor use in relation to referrals. Regarding CVMP’s view on the future legislation, please see *The CVMP analysis of the functioning of current veterinary legislation and proposals for its evolution and comments on the Commission paper* (EMA/CVMP/463298/2010 from July 2010).

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105/109 and 112/113 (and line 35)	6	Comment: As above, encouragement is very much appreciated. However, we request that CVMP explains in more detail what it will do that will provide companies with the incentive to invest in narrow spectrum antimicrobials or different formulations. Furthermore we request that CVMP keeps in mind that narrow spectrum antimicrobials are only suitable for narrow spectrum infections. In many diseases, there are mixed infections or multi-causal diseases. It is more reasonable to stress the principle of therapy based on prior diagnosis. The necessity to have broad spectrum AM in cases of life threatening diseases should be kept in mind, as quick action has to be taken for animal welfare and results of susceptibility testing will not be available quickly enough. In such situations, broad spectrum antimicrobials are needed and are advantageous. Proposed change: CVMP should provide clarification on the type of encouragement and additional regulatory actions that can be implemented to support innovation. The document talks about encouraging innovation but the content of the chapters elsewhere reflects on banning availability of molecules with new mode of actions in the veterinary market which seems highly contradictory.	We cannot be more specific at present but would like to stress that our intension is to support such innovations to the extent we can. We fully support the principle of therapy based on prior diagnosis. As detailed above we acknowledge that the need for innovation in veterinary medicine and the possible need to restrict the use of some last resort medicines for man constitutes a dilemma.
117-128 (also 218-	6	Comment: CVMP states that in some cases the same antimicrobial molecule should not be developed for both	We fully agree that decisions must be taken on a case by case basis following adequate risk analysis. When doing so, cross-

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221)		human and veterinary use. However, many of the existing products do have “dual use” and have been managed satisfactorily (e.g. penicillin, tetracycline, erythromycin, etc.). Innovation should not be stifled by restricting entire antibiotic classes from commercialisation due to the perception of cross-resistance, but rather evaluated on an individual molecule basis for within-class candidates. There is a contradiction between the call for innovations on the one hand and restrictions on new chemical entities that may have a use in human medicine on the other hand. Will an AH company be able in the future to register and market a new compound class or new candidate compound from an existing compound class which is also developed/ marketed by human pharma, provided that there is no significant epidemiological overlap between the claimed human target pathogens? Proposed change: After line 124 add: Innovation should not be inhibited by restricting entire antibiotic classes from commercialisation due to the perception of cross-resistance, but will be evaluated on an individual molecule basis for within-class candidates.	resistance will be assessed as one aspect. We cannot ensure that it will never be the case that a complete class of antimicrobials will be found to have a negative benefit/risk balance. Until the assessment is made in the certain case (following scientific advice or marketing authorisation applications) no such conclusion could be drawn.
127	6	Comment: CVMP is requested to specify what risk assessment process will be followed. Proposed change: …risk assessment (see OIE Terrestrial Animal Health Code 2010 Chapter 6.11.1)	Please see above, See also *Recommendations on the evaluation of the benefit-risk balance of veterinary medicinal products* (EMEA/CVMP/248499/2007 from April 2009).

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131	6	Comment: An early dialogue is very much appreciated, to get advice and binding information on the development of e.g. new antibiotic classes.	Agreed.
151	6	Comment: The terms “highly contagious and severe diseases” are somewhat imprecise. Proposed change: We suggest “……..should be limited to diseases and outbreaks where significant morbidity and mortality is anticipated”	We would regard “significant morbidity and mortality” imprecise as well. However, it is up to each veterinarian to determine when the spread of disease is so rapid that treatment of all animals is necessary.
151-154	6	Comment**:** Blanket statements regarding oral administration fail to recognise the necessity of group medication, such as for poultry where drinking water is often the only option. Although concerns are raised that oral administration is not well-controlled (i.e. doses of individuals in the population may vary), population pharmacokinetics aim for at least 90% of the individuals to consume an appropriate therapeutic dose. In contrast to this dosing concern for AMR, it has been stated to be of little to no concern by the CVMP/EMA working group on bioequivalence as it is not required to demonstrate in vivo equivalence for in feed or in water products. These products are given categorical exclusions from in vivo demonstration of BE, so to raise this concern here is in direct contradiction. Proposed change: Delete line 151-154 (Oral products…will be high) and replace with: Oral products for group or flock medication are of limited concern; especially in light of the lack of regulatory concern	The CVMP does not agree with the comment. In feed medication is not categorically excluded from *in vivo* bioequivalence and few approved products are supported by appropriate population pharmacokinetic data. In all cases oral treatment is of special concern as many AMR related hazards are gastrointestinal tract bacteria. We remain of the opinion that solutions for drinking water and highly soluble compounds mixed with feed components could be accepted as biowaivers for bioequivalence studies and we do not understand the relation with the higher risk for AMR estimated for oral products for group medication.

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		regarding BE for generic products.	
154-156	6	Comment: It is not clear what this sentence is intended to convey. It requires clarification.	Some antimicrobials are effective as growth promoters. It might be an economical advantage of using such products for this purpose although it is not allowed.
172	6	Comment: Clarification is needed on this point, for the definition of “unnecessary use”.	Any use which is not needed. Routine prophylaxis in herds without an ongoing infection would be an example.
185-187	6	Comment: Well established products are those with long field experience. Safety and efficacy have been proven over several years in the field. This should be taken into account when evaluating these products.	Yes, it is taken into account as discussed in the guidance on (fluoro)quinolones[1] and cephalosporins[2] respectively. Note that it is the level of safety that has been proven. All antimicrobials select for resistance and although well established products are well known it doesn’t mean that they are safer.
193-202 194-198	6	Comment: This section needs to be further clarified so as to not require non-applicable chapters of the OIE Terrestrial Animal Health Code to apply to pivotal clinical trials. As well, what pivotal clinical trials are to be included? It should be kept in mind that a product needs to show clinical efficacy in the field and activity against a specific disease agent (the target bacterium). Whether the product should be used as first-line or second-line treatment has to be defined in the SPC, not in the pivotal study, otherwise the set up of a clinical trial in the field would not be manageable. This implies that	The comment is not fully understood. This could be further elaborated when revising the guideline on efficacy of antimicrobial products.

[1] http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500005152
[2] http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004307

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199-202		one first needs to await demonstrated treatment failure before being able to include an animal in the study. While this may render a clinical study impossible, it would also have severe consequences for animal welfare. Proposed change: Delete sentence from 196-198 Self-cure assessment must not only consider survival but also economic losses due to non treatment (e.g. growth retardation, milk losses) and return rates to infections (relapses). Animal welfare aspects have also to be taken into account. Proposed change: As much as possible with the regulatory pivotal effectiveness trials, the OIE Terrestrial Animal Health Code 2010 Chapter 6.10. should be followed.	
207-217	6	Comment: It is not clear whether VICH GL27 is to be followed and CVMP will then do a benefit:risk assessment OR if the medicine sponsor needs to complete both. As well, the benefit:risk assessment guideline is presumed to be that of OIE Terrestrial Animal health code 2010 Chapter 6.11.1. Clarity on the approval/non-approval criteria is needed by companies to estimate the likelihood of product candidate regulatory success. Proposed change: CVMP needs to clarify what the risk evaluation guidelines are, what organisation completes	The GL27[3] and the *Recommendations on the evaluation of the benefit-risk balance of veterinary medicinal products* (EMEA/CVMP/248499/2007 from April 2009) will be followed. In addition, the need for further guidelines will be considered.

[3] http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004308

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		them and what the approval/non-approval criteria are.	
218-221 (also 122-124)	6	Comment: See comment regarding line 122-124. For the elaboration on the need for further guidelines, we recommend a clarification to which extent new classes/new modes of action can be developed and registered for veterinary medicine as they are developed for human medicine or might be developed for human medicine at a later stage or by a different party.	Advice can be given on a case by case basis only. Please seek scientific advice when in doubt.
226	6	Comment: CVMP might consider joint training with assessors and industry	Coordination of training of assessors is currently being investigated and developed in the Network and new modes of training may become available in the future.
301-304	6	Comment**:** It is the remit of the European Commission to rethink generic access to the antimicrobial veterinary market	Agreed.
305-310	6	Comment: the formulation of the paragraph gives the impression that CVMP defines Responsible use as Reduced use. The impact of the measures taken to promote prudent use can only be correctly assessed if “context” information is also collected, i.e. other factors, such as a major outbreak of disease, that affect the use of antimicrobials. Proposes change: Please add a statement recognising the need to collect “context” information, so that the sales data can be correctly interpreted.	CVMP is well aware of the need to consider different factors when interpreting figures of sales of antimicrobials.
311-315	6	Comment: IFAH-Europe is favourable to support a	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		target pathogen monitoring program (TPMP) in cooperation with national authorities, based on a European-wide harmonized protocol for sampling, testing and interpretation criteria and identical definitions of resistance. All antibiotic marketing companies should be required to contribute. Proposed change: Line 315, please replace “”diagnostic tools” by “methodology”.	
316-319 (esp. 318-319)	6	Comment: The Codex Guidelines for Risk Analysis of Foodborne AMR are designed to apply to food safety and are not intended to be applied as a regulatory medicine approval process. This is clearly evident within the document because any issue related to medicine registration is directed to national regulatory authorities and the OIE Terrestrial Animal Health Code chapter 6.11.1 on risk assessment. Proposed change: Delete Codex Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance and replace with OIE Terrestrial Animal Health code 2010 chapter 6.11.1	The context here is wider than approval processes as the text is on an overall EU strategy on antimicrobial. Food safety risk assessment fit into this wider context.
320-322	6	Comment: We appreciate the project on quantification of impact and want to offer assistance for this endeavour	Thank you.
329-331	6	Comment: ESVAC data needs to provide context data as well as sales data.	The comment has been forwarded to the ESVAC for consideration.

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129-133	7	**Action 2. Innovation on treatment alternatives**. We wonder whether it would be possible for CVMP to go further and facilitate discussions to identify gaps? Presumably dissemination of this information would be agreed at the time.	To be considered.
175-191	7	**Action 3. Product information on selection pressure for AMR.** Extending the warning sentences to certain products containing cephalosporins is a useful step. Macrolides are important in human medicine and actions should be considered in the same way as for the fluoroquinolones and cephalosporins, which will encompass the WHO's critical groups.	CVMP is about to publish a reflection paper on macrolides.
203-204	7	**Action 4. Clinical trials**. An impact assessment in consultation with industry will be needed to ensure that special study designs (e.g. investigating second line treatments) are not prohibitive in terms of time taken to recruit sufficient cases, and therefore may deter new applications on the grounds of increased costs. This should also consider if the need to include placebo controls (as proposed in the concept paper for the GL on antimicrobial efficacy) will cause recruitment/welfare issues and difficulties in obtaining clinical trial approvals from NCAs	A draft of the revised guideline will be published for consultation.
222-226	7	**Action 5. Risk mitigation at a proportionate level**. This is considered to be an important step, which we fully support. As an example, carbapenemases are having a significant impact on human health in some countries and given the known human impact of other	We are not ready to draw general conclusions on a certain group of antimicrobials. In case an application for a carbapenem is submitted or if a company ask for scientific advice for such a product we would carefully consider AMR

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		B-lactam resistances on the rate of development of carbapenem resistance it would be prudent to not permit their authorisation in VMPs.	risks when assessing the product.
250-260	7	**Action 6. Off label use.** Cascade restrictions need to be considered very carefully to ensure welfare issues are not created. If a vet is legally prevented from using a product know to be effective for particular diseases, they will potentially be presented with a choice of breaking the law or euthanizing the animal. It is essential that all aspects of the practicality of restricting use via the cascade are taken into account. For example, how will enforcement be achieved?	Agreed.