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4 CVMP strategy on antimicrobials 2016-2020

5 Draft

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Introduction

The CVMP is responsible for preparing opinions on marketing authorisations for veterinary medicinal products and in this respect one of its key objectives is to promote the availability of effective antimicrobial veterinary medicines in order to protect animal health and welfare. This objective is threatened by the challenge of antimicrobial resistance (AMR) and, by providing guidance to ensure the responsible use of antimicrobials in animals, the CVMP has an influential role to play in minimising the risk that AMR presents not only to animal health and consequently to food security, but also to human health.

Much has been achieved since the CVMP's previous strategy on antimicrobials was published in 2011 (see Annex). Working collaboratively with its stakeholders, the CVMP has made good progress towards updating its scientific and regulatory guidance documents. The CVMP has also taken steps to address the risks to public health from the use of critically important antimicrobials in food-producing species by implementing risk management measures into the Summaries of Product Characteristics (SPCs) for systemically administered 3rd- and 4th-generation cephalosporins and orally administered colistin products. In addition, reflection papers and recommendations have been published on the use of macrolides and lincosamides, and of pleuromutilins, in food producing animals. The CVMP has also considered the increasingly recognised risk of transfer of AMR from companion animals to humans in its reflection papers. With respect to animal health risks due to evolving AMR, the CVMP has undertaken more than 20 referral procedures affecting 6 classes of antimicrobials, reviewing indications, dosing regimens and responsible use warnings and introducing updates to Marketing Authorisations to ensure that antimicrobial veterinary medicines on the market maintain a positive benefit-risk balance.

However, in the last 5 years there has been increasing political awareness of the problem of AMR and the need to take urgent action, with both the European Parliament (2012, 2015) and the Council (2012) publishing their positions and emphasising the need for a One Health approach, recognising the interconnection between animal health, human health and ecosystems. Earlier, in 2011, the European Commission launched its 5 year Action Plan against Antimicrobial Resistance, the overall aims of which are to reduce and prevent the spread of AMR and to preserve the ability to combat microbial infections. The plan included several actions which will result in outcomes that will impinge directly upon the work of the CVMP over the coming years.

Foremost is the adoption of a proposal for a new Regulation on Veterinary Medicinal Products, which is currently undergoing legislative procedure through the European Parliament and Council. This proposal contains provisions that aim to strengthen the benefit-risk assessment for antimicrobial veterinary medicinal products, provide a legal tool to preserve certain antimicrobials for human use and strengthen controls around their use under the cascade[1]. In addition, in 2014, the EMA/AMEG provided advice to the Commission on the impact on public and animal health of the use of antibiotics in animals[2]. Recommendations were made including a categorisation of human critically important antimicrobials with guidance on the level of restriction that should be placed on their use in veterinary medicine in order to limit the risk to public health. Although the need for new antimicrobials for veterinary medicine was recognised, it was recommended that their use should be accompanied by a reinforced risk assessment taking into account the risk to public health.

[1] See article 10 and 11 of the Directive 2001/82/EC of the European Parliament and of the Council as amended.

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000639.jsp&mid=WC0b01ac058080a585

It is against this background, although with some uncertainty pending adoption of the veterinary medicinal products Regulation and agreement of its implementing acts, that the CVMP has prepared its strategy for the next 5 years to 2020.

CVMP Vision Statement on antimicrobials[3] 2016-2020

The CVMP's vision is the availability of effective antimicrobial medicines for the treatment of important infectious diseases of animals with, at the same time, minimum risks to animals or humans arising from their use.

Summary of the CVMP strategy on antimicrobials 2016-2020

- Aim 1: To provide opinions for the **authorisation of effective antimicrobial veterinary medicinal products** ensuring that the necessary **risk management measures** are applied so that products can be used safely and sustainably.
- Aim 2: To consider and advise on the **risk to public health** that could arise from the use of antimicrobials due to the transfer of antimicrobial resistance from animals to humans, and to balance this against the need to protect animal health.
- Aim 3: To **maintain the effectiveness** of antimicrobial substances that are **already authorised in veterinary medicinal products** by monitoring and analysing their **sales and usage**, encouraging **surveillance for changes in susceptibility** of target pathogens and zoonotic bacteria, and subsequently **reviewing the authorisation** of substances and/or products, especially when there is evidence that there may be a related change in the benefit-risk of the authorisation.
- Aim 4: To encourage the **development of new and existing antimicrobial veterinary medicinal products**, especially in order to **fill therapeutic gaps** and for **minor uses and minor species**, and to foster the development of **alternatives to antimicrobials**.
- Aim 5: To support the **responsible use** of antimicrobials both in accordance with Marketing Authorisations and under the **cascade**.
- Aim 6: Recognising that **AMR is a global problem** affecting both animal and human health, to work in partnership with the European Commission, international regulatory bodies, human and animal health organisations and the pharmaceutical and livestock industries to provide science led guidance on the responsible use of antimicrobials in animals.

It is the CVMP's responsibility to provide clear guidance on the data required to support applications for marketing authorisations for antimicrobial veterinary medicinal products (VMPs). In updating its **Guideline for the demonstration of efficacy veterinary medicinal products containing antimicrobial substances**, the CVMP has taken account of scientific advances in areas such as dose-finding, has highlighted how product development should be consistent with principles of "responsible antimicrobial use" and given further guidance on study design for claims for metaphylaxis and prevention of disease. New guidance is also under development on the data requirements and approach to be taken for the assessment of the **risk to public health from the use of antimicrobial VMPs in food-producing species**. With further consideration to public health, the CVMP supports the **categorisation of human critically important antimicrobials** provided by the AMEG and the

[3] OIE definition "Antimicrobial agent": *"means a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition."* (http://www.oie.int/fileadmin/Home/eng/Health_standards/tahc/2010/glossaire.pdf)

establishment of a list of specific substances which are of **last resort for treatment of life-threatening disease in humans and should be excluded from veterinary use**. However, it is also recognised that the greatest driver of AMR in people is the use of antimicrobials in human medicine and CVMP considers that risk management measures applied to VMPs should be proportionate and evidence-based. It is hoped that the new guidance will provide greater transparency for pharmaceutical companies considering antimicrobial product development and address the lack of "regulatory uncertainty" that has been identified as a contributor to the recent limited development of antimicrobial veterinary medicines.

The CVMP supports the development of new antimicrobial VMPs; however, in order to slow the development of antimicrobial resistance resulting from over-reliance on single substances, a range of antimicrobial agents should ideally be available for use in veterinary medicine. This means that **substances that are already authorised must be used sustainably and the conditions of use provided in the SPC should support this**. Through referral procedures the CVMP is responsible for reviewing Marketing Authorisations and past experience has shown that up-to-date SPC guidance often cannot be based only on the data available from old dossiers. The CVMP should have the flexibility to make use of the latest scientific knowledge and developments when conducting these procedures, for example in respect of reviewing dosing regimens and for subsequent adjustment of withdrawal periods, in order to avoid loss of older antimicrobial products or species and indications. Further refinement of the **ESVAC**[4] data collection to include information on species and usage, coupled with **improved surveillance for AMR** including in target pathogens, should allow the CVMP to better focus risk management measures. Recent referrals have implemented risk mitigation measures based on profiling of antimicrobial classes developed in papers from the CVMP and its Antimicrobial Working Party (AWP) and the Antimicrobial Advice ad hoc Expert Group (AMEG). The CVMP will continue to address emerging AMR issues and, following the recommendations of the AMEG, risk profiling will now be undertaken for the **extended-spectrum Penicillins** and **aminoglycosides**.

It is probable that one of the most effective measures to limit expansion of AMR is an **overall reduction in antimicrobial use**. This is best achieved through measures to prevent infections from establishing (husbandry, biosecurity, vaccination, etc) and more **targeted use** of antimicrobials where it is still necessary to guard animal health (e.g. by use of accurate diagnosis, evidence-based regional treatment guidelines and correct dosing regimens). It is recognised that **group metaphylaxis** accounts for a high proportion of veterinary antimicrobial use and in order to support a more reasoned approach the CVMP will endeavour to provide improved SPC guidance about the epidemiological circumstances under which this has shown to be effective and the extent of benefit demonstrated. The CVMP will also **support the development of veterinary medicines which reduce the need for use of antimicrobials ("alternatives")**, such as vaccines, and will facilitate the regulatory pathway for innovative products by contributing guidance through the Innovation Task Force (**ITF)** and the CVMP Ad Hoc Group on Veterinary Novel Therapies (**ADVENT)**.

The CVMP recognises the value of the **cascade** to allow treatment of diseases for minor uses and minor species, acknowledging that the cost of development inevitably leads to limited availability of veterinary medicinal products authorised for species and indications representing smaller market sectors. However, it has also been acknowledged that more convenient formulations of older, narrow spectrum Category 1 (lower risk)[5] antimicrobials for treatment of common indications could more

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

[5] Category 1: antimicrobials used in veterinary medicine where the risk for public health is currently estimated as low or limited. Includes some classes of antimicrobial that have widespread use in veterinary medicine, and also include substances which are regarded as first choice in many treatment guidelines. These are certain penicillins, tetracyclines, macrolides and polymyxins. For further information see http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf

generally **reduce the use of critically important antimicrobials and off-label use** that results solely due to the access and easier compliance associated with modern formulations. Where interest is shown by industry, the CVMP, in conjunction with its various working parties, will **provide advice to facilitate development of such products as well as those for MUMS/limited markets**.

Finally, the CVMP recognises that AMR is an expanding global problem affecting both animal and human health. Therefore it is important that the **CVMP continues to work with colleagues in the EU network agencies, international regulatory bodies and with its stakeholders** to ensure harmonisation of regulatory frameworks and that a One Health approach is taken to the control of AMR.

CVMP'S Strategic aims and proposed actions in relation to antimicrobials 2016-2020

1. Provide opinions to support the authorisation of effective antimicrobial veterinary medicinal products with measures ensuring safe and sustainable use

The CVMP's **guideline on the conduct of efficacy studies for antimicrobial VMPs** has recently undergone extensive revisions to address the need for product development to be consistent with the principles of responsible use of antimicrobials and to take advantage of advancements in areas such as dose-finding. The revised guideline highlights that indications for VMPs should be justified in the context of the need to reserve critically important antimicrobials for certain conditions, as already outlined in the CVMP's reflection papers, for example on fluoroquinolones, 3rd- and 4th-generation cephalosporins. This context should also be taken into account in the design of the supporting studies. The dose and duration of treatments must be supported by pre-clinical and clinical data with consideration given to both efficacy and the need to minimise AMR development.

The revised guideline also introduces guidance on study design for claims for **metaphylaxis and prevention** of disease. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) data from 2013 showed that premix, oral powder and oral solution formulations made up 91.5% of antimicrobial sales (mg/PCU) for livestock. Although some of this use is for treatment of clinically ill animals, it is also recognised that a high proportion will be for metaphylaxis of disease. The need for metaphylaxis to minimise the consequences on herd health from diseases which are highly contagious and severe is recognised; however, claims for such indications should always be fully justified on clinical and epidemiological grounds.

Claims for **preventive use** of veterinary antimicrobials should only be considered in situations where the risk for infection is very high and the consequences are severe; or as part of recognised eradication programmes. Antimicrobials should never be used preventatively to compensate for the impact of husbandry systems or a lack of biosecurity.

A discussion of further risk management measures is included under Aim 3.

CVMP's proposed actions:

- The CVMP will finalise and implement the revisions to the **guideline on the demonstration of the efficacy** of antimicrobial VMPs.
- We will provide precise and thorough information in the **SPC** about the extent and limits of the benefits that can be expected to arise from **metaphylactic treatment** in a flock/herd to give the product user realistic expectations and thereby reduce unnecessary antimicrobial use.
- We will provide **training to assessors** in the application of CVMP guidance documents relating to antimicrobial VMPs.

2. Consider and advise on the risk to public health of the use of veterinary antimicrobials and to balance it against the need to protect animal health

A clearly stated objective of the proposed Regulation on VMPs is to address the public health risk of AMR arising from the use of antimicrobials in veterinary medicine. In 2014, the EMA published scientific advice to the European Commission on the impact on public and animal health of the use of

antibiotics in animals[6]. This advice is part of the EC's *Action Plan against the rising threat from AMR* and, taking a **One Health** approach, was jointly developed by the CVMP, the Committee for Medicinal Products for Human Use (CHMP), the European Centre for Disease Prevention and Control (ECDC), and the European Food Safety Authority (EFSA). It includes a **categorisation of human critically important antimicrobials,** based on that of the World Health Organization (WHO), according to the risk to humans due to AMR development following their use in animals. The advice recommended that for antimicrobials in Category 1 (low/limited risk), general principles of responsible use should be applied; whilst those in Category 2 (higher risk) which includes fluoroquinolones and systemically acting 3rd- and 4th-generation cephalosporins, should be used only where there are no alternative antimicrobials authorised for the given species and indication. It was also recommended that for both aminoglycosides (increasingly used to treat infections due to multidrug-resistant *Enterobacteriaceae* in humans) and certain broad-spectrum penicillins (which may select for extended spectrum beta-lactamase-producing *Enterobacteriaceae*), further risk profiling was required.

Further to this, the CVMP agrees that specific human critically important antimicrobials which are of **last resort for treatment of life-threatening disease in humans should be excluded from veterinary use** where this measure is supported by the findings of an assessment of the hazard and consequences to human health.

The categorisation discussed above is at the level of substances/classes of antimicrobials and does not take into account the conditions of use (e.g. route of administration) that apply to a specific product. The CVMP is now preparing further **guidance for industry on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals**. This guidance builds upon that already provided in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline 27, but considers further the exposure of zoonotic and commensal bacteria in the target animal species based on the conditions of use of the VMP, the probability of subsequent human exposure to AMR and the resulting consequences to human health. An acceptable level of risk is that which, when weighed against the proposed benefits of the use of the veterinary medicinal product in the target species, will not significantly compromise therapeutic use of antimicrobials in humans or human health. However, it is recognised that the biggest driver of AMR in people is the use of antimicrobials in human medicine. The CVMP identifies the continued need to use antimicrobials in the interests of animal health and welfare and considers that the risk management measures applied to VMPs in order to address any public health risk should be proportionate and based upon robust scientific evidence.

Food has always been identified as an important route through which human beings may be exposed to certain types of resistant bacteria; however, the CVMP recognises that close contact between **companion animals** and their owners also offers an opportunity for direct transfer of AMR about which there is currently limited knowledge. A reflection paper and recommendations on this topic were published in 2014.[7]

The importance of the **environment as a reservoir for antimicrobial resistance genes** is now widely recognised. Use of antimicrobials in animals, including in aquaculture, leads to contamination of the environment both with antimicrobials and resistant bacteria. The presence of antimicrobials in the environment exerts a selective pressure for resistance genes in bacteria in a variety of ecosystems including animals, humans and plants. The cycling of these resistance genes between the different ecosystems is extremely complex and requires further research. The CVMP acknowledges that further

[6] Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals. See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/07/WC500170253.pdf
[7] Reflection paper on the risk of antimicrobial resistance transfer from companion animals. See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500181642.pdf

consideration should be given to the contribution of veterinary antimicrobial use to the environmental resistome.

CVMP's proposed actions:

- We will provide advice to the European Commission as it develops and implements those parts of the new **Regulation on Veterinary Medicinal Products** and its technical annexes that relate to antimicrobial VMPs and use of antimicrobials in animals. On request from the Commission, the CVMP will contribute to the establishment of a **list** of antimicrobial substances which should be **reserved for treatment of human infections only**. A One Health approach will be taken to establishing the list.
- We will finalise the **guideline on the assessment of the risk to public health from AMR due to the use of an antimicrobial veterinary medicinal product in food producing animals**, taking into account the scientific advice to the European Commission (AMEG) and comments received during public consultation for the guideline.
- Once experience is gained in the future following application of the guideline (above) as it applies to products for food-producing species, the CVMP will consider developing further guidance for industry on the assessment of the risk to public health from antimicrobials intended for **companion animals**.
- The CVMP will conduct risk profiling for **aminoglycosides** and **extended-spectrum penicillins** and make recommendations for risk management measures, as needed.
- The CVMP will contribute to the request from the Commission for a **Joint EFSA / EMA Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety**.
- The CVMP will develop a reflection paper to consider the role of **AMR in the environment** and the feasibility of addressing this in the environmental risk assessment for veterinary medicinal products.

3. Take measures to ensure continuing effectiveness of authorised veterinary antimicrobials

The CVMP recognises the need to maintain the effectiveness of antimicrobials in order to protect animal welfare and ensure healthy livestock to support food security.

Under the Zoonoses Directive, data on AMR in zoonotic and indicator bacteria from food animals are already monitored by EFSA due to concerns about the potential impact on public health. The CVMP welcomes initiatives from industry and authorities for the surveillance of AMR in animal pathogens. In addition, at the time of authorisation of an antimicrobial substance that is new to veterinary medicine, information may not be available to fully assess the risk for AMR emergence. Therefore, for new antimicrobial substances the marketing authorisation holder should be encouraged to have in place plans to monitor the **evolution of susceptibility in target pathogens,** including sampling based on a scientifically determined protocol and susceptibility testing using standardised methodology (where available).

Since 2009, the EMA has collected data on sales of veterinary antimicrobial products from EU member states and EEA countries under the **ESVAC** project. These data are of value for assessing the exposure of animals to antimicrobials, which is an essential part of risk assessment and for monitoring the effectiveness of responsible use campaigns. It is anticipated that future refinements in the data

collection to usage at species level, and also taking into account the dosing of the antimicrobials and the number of treatment courses administered, will enhance the usefulness of the data in this respect.

The **SPC / product information** is the regulatory tool which specifies the conditions for antimicrobial VMPs to be used effectively and communicates risk management measures allowing for safe use and to minimise the development of AMR. As such, it is the CVMP's key means of communication with the veterinary prescriber. Indications should be worded to clearly express the intended use of the product and general indications (those that do not include named target pathogens) should be avoided. Clear directions should be provided to avoid sub-therapeutic dosing and the duration of treatment should be limited to the time needed for the cure of disease. Pharmacokinetic and pharmacodynamic data, clinical break-points (where available) and information on known mechanisms of resistance should be included to allow for informed prescribing.

The CVMP acknowledges that there are some **long-used antimicrobials** whose SPCs are inconsistent with responsible use principles, or that have dosing regimens that are not compatible with modern pharmacokinetic/pharmacodynamic concepts or the evolution of pathogen susceptibility since the time of authorisation. These products should be addressed by scientific re-assessment. The CVMP has already conducted several **referral procedures under Article 35** of Directive 2001/82 EC of the European Parliament and of the Council as amended, based either directly on evidence of a change in AMR risk factors or on risk profiling published in its reflection papers. After re-evaluating the benefit-risk for affected products, the consequence of such referrals has been to place restrictions on use, e.g. by removing indications or target species where data do not support use, and strengthening warnings for responsible use. Further consideration could be given to developing methods to review dosage regimens and for subsequent adjustment of withdrawal periods in order to avoid loss of species and indications from older antimicrobial products during such procedures. Products which contain **combinations of antimicrobial substances**, especially if these include critically important antimicrobials, are of particular concern if their goal is to bypass the need for accurate diagnosis and where they are intended for mass medication.

The CVMP believes that risk mitigation measures for antimicrobial VMPs should be based on scientific risk assessment, that they should be proportionate and that any potential negative impacts on animal health and welfare must be taken into account. However, it is problematic that the effectiveness of individual risk mitigation measures has in most cases yet to be evaluated in terms of economic impact or benefits to animal or public health. Investigating a link between antimicrobial usage in animals and AMR in humans is hindered by the complexity of transmission routes and ecological aspects of the selection pressure for resistant bacteria. In addition, even if a link is established, taking action on one antimicrobial class may not automatically impact the level of resistance to that class due to cross and co-resistance mechanisms. The CVMP therefore supports **measures to reduce the overall consumption of antimicrobials in animals**, in line with responsible use principles. In order to achieve this, a holistic approach should be taken as outlined in the EC's [proposed] Animal Health Law which focuses on prevention of disease in order to reduce the reliance on antimicrobials (e.g. through Salmonella control programmes). Use of vaccination and husbandry measures to promote animal health and improve biosecurity are also vital.

CVMP's proposed actions:

- The CVMP will ensure that when assessing veterinary medicinal products authorisations, best use is made of available data on the **susceptibility of target pathogens.**
- The CVMP will consider the need for **post-authorisation data** to be provided and reviewed (e.g. as outlined in CVMP's reflection paper on AMR surveillance as post-marketing authorisation commitment[8] in order to ensure that the benefit-risk balance remains positive with respect to the possible development of AMR.
- The CVMP will support the collection of data on antimicrobial consumption (sales and use) under **ESVAC** and take into consideration the findings of the analysis of these data and data from **EFSA's** surveillance programmes for zoonotic pathogens and indicator bacteria from humans, animals and food when providing opinions.
- The CVMP will review the Marketing Authorisations of existing antimicrobial VMPs, by means of **referral procedures**, where there is evidence that there may be a change in the benefit-risk that requires new risk mitigation measures to be applied, or changes to dosing regimens etc. Through these procedures, CVMP will provide scientific assessment for long-used antimicrobial products to enable **harmonisation and updating of the SPCs and aim to avoid loss of older antimicrobials from the market where these are still useful**.
- The CVMP will continue to provide **reflection papers** on topics relating to the need, use and development of resistance to veterinary antimicrobials and will make recommendations based on these papers.
- The CVMP will consider the potential benefits to veterinarians and to animal health of routinely establishing veterinary **clinical break-points** for antimicrobials. CVMP will consider the practical arrangements, the potential impact on data requirements and the implications for new and existing marketing authorisations.

4. Encourage the development of antimicrobial veterinary medicinal products, especially for minor uses and minor species, and foster the development of alternatives to antimicrobials

In 2015, although resistance in veterinary pathogens is acknowledged as an increasing problem, there are a limited number of important infections in the major veterinary species in the EU where there are no, or very restricted, treatment options due to AMR. Examples provided by stakeholders of indications for which new antimicrobials are needed include *Brachyspira hyodysenteriae* in pigs, methicillin-resistant *Staphylococcus pseudintermedius* in dogs and certain coliform infections (AMEG, 2014). Despite this, the CVMP supports the **development of new antimicrobial VMPs** as the availability of antimicrobials from a range of different classes will help to reduce the over reliance on a small number of substances which may accelerate the development of resistance. For all new antimicrobial VMPs, authorisation should be based on a benefit-risk assessment that demonstrates that there is an acceptable risk to public health, taking into account the benefit to animal health and welfare. The revisions to the Antimicrobials Efficacy guideline and introduction of the CVMP's Risk Assessment guideline for antimicrobial VMPs are aimed at reducing the regulatory uncertainty that acts as a barrier to the development of new antimicrobial products. The regulatory path for novel products including **alternatives to antimicrobials** is also supported through the Innovations Task Force and the CVMP's ADVENT (Ad Hoc Expert Group on Veterinary Novel Therapies) group.

[8] Antimicrobial-resistance surveillance as post-marketing authorisation commitment (EMEA/CVMP/SAGAM/428938/2007). See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005150.pdf

Although the prospect of new antimicrobial classes for use in veterinary medicine seems limited, the CVMP recognises that there could be an opportunity to develop **new formulations of older Category 1 narrow spectrum antimicrobials** that would be suitable for veterinary patients and carry a reduced risk to health due to AMR. Such products could reduce the use of critically important antimicrobials and off-label use that results solely due to the access and easier compliance associated with modern formulations. In addition, although there is a need for effective antimicrobials to treat certain minor uses and minor species, this could most often be met by expanding indications for existing products, or developing new products based on old antimicrobial classes. The CVMP will promote that the regulatory environment facilitates the development of these types of products.

CVMP's proposed actions:

The CVMP wishes to contribute to a predicable regulatory environment that encourages investment in developing veterinary antimicrobials by producing guidance clarifying as far as possible the requirements that will need to be met to bring new veterinary antimicrobials to market. In addition to new and updated GLs already mentioned, the CVMP will:

- Provide regulatory guidance through the **Innovation Task Force** and **ADVENT** group, and **scientific advice** on request from marketing authorisation applicants on the development of new antimicrobial products, and alternatives to antimicrobials for the treatment of microbial infections
- The CVMP will reflect further on measures that could be taken to promote the development and access to market of alternatives to antimicrobials, giving particular attention to **vaccines** as part of the current initiative to promote availability of products that can reduce the need for antimicrobial treatment within the EU.
- The CVMP will consider the benefits of developing a list of minor uses and minor species indications for which there are currently therapeutic gaps and for which development of antimicrobial or alternative products should be encouraged.
- The CVMP will continue to take into consideration the **minor uses and minor species guidelines** when reviewing marketing authorisation applications for designated products and consider if this guidance can be revised to include specific advice for antimicrobials.
- In particular, and taking into account the AMR risk, the CVMP will support expanding of indications, species and formulations for existing products, especially those including antimicrobial substances included in **Category 1**.

5. Support the responsible use of antimicrobials both in accordance with Marketing Authorisations and under the cascade

The responsible use of antimicrobials in veterinary medicine is a key element of the *EC's Action Plan on AMR.*

Antimicrobials should only be used following accurate clinical evaluation and diagnosis involving use of relevant bacteriological sampling when required. Only the required quantity should be supplied for the treatment course and appropriate risk management measures should be taken into consideration for prescribing. The CVMP will therefore continue to provide opinions on antimicrobials on the basis that they should remain available only on **veterinary prescription**.

The development and implementation of evidence-based national and **regional treatment guidelines** is encouraged. An SPC drafted in accordance with the CVMP's guideline on the SPC for Antimicrobial Products should provide essential background information for those compiling treatment guidelines.

Treatment guidelines can also support appropriate off-label use of antimicrobials by taking account of the local AMR situation, risks to animal and public health and product availability in the member state.

The importance of the Cascade to address unmet needs will be addressed in a CVMP reflection paper on the **"off-label" use** of antimicrobials in animals. However, there is currently no official systematically collected data on the extent of this practice and therefore very little evidence on which to base a general assessment of the risk due to AMR that off-label use could pose to animal and public health. The **cascade use** of antimicrobial substances presently only authorised for human use is restricted to non-food animals only provided that the substance does not have an MRL (maximum residue limit). In addition, the proposed Regulation on Veterinary Medicines will empower the European Commission to limit the use of certain antimicrobials in animals to use in accordance with the terms of the Marketing Authorisation.

CVMP'S proposed actions:

- The CVMP will provide guidance for industry on the appropriate **pack-sizes** for antimicrobial veterinary medicinal products so that they are aligned with the treatment course, so facilitating responsible prescribing.
- The CVMP will provide a **reflection paper on the off-label use** of antimicrobials in veterinary medicine and make recommendations for risk management measures to promote responsible use of the cascade.
- The CVMP supports the development of **evidence-based national and regional treatment guidelines** which take account of local trends in antimicrobial sensitivity, animal health status and product availability. The CVMP will aim to ensure that advice provided in SPCs facilitates the development of such guidelines.

6. Work in partnership with EU and international human and animal health organisations to tackle the global problem of AMR

The EU has a benefit/risk-based approach for the authorisation of antimicrobial VMPs and is currently developing systems for monitoring of antimicrobial consumption/usage and surveillance for AMR. However, it is predicted that antimicrobial consumption worldwide will increase in line with the growth in demand for animal protein; this increased use will present a particular opportunity for the development of AMR and a risk to animal and public health in countries with less well developed regulatory systems. When this is coupled with increasing international trade and travel, it is clear that AMR is an expanding global issue. Recognising the need for collaboration between human health, animal health and agricultural sectors, the WHO has published a draft Global Action Plan, which outlines the roles and responsibilities of stakeholders in relation to AMR. The overall public health goal of the action plan is to ensure, for as long as possible, continuity of treatment and prevention of infectious disease with effective safe medicines that are quality-assured, used in a responsible way and accessible to all who need them. A number of International intergovernmental bodies and EU industry and professional organisations such as WHO, World Organisation for Animal Health (OIE), Codex Alimentarius, EFSA and Federation of Veterinarians of Europe (FVE) already produce guidance on risk assessment and responsible use recommendations. It is important that the CVMP continues to collaborate with international bodies such as VICH and Codex to harmonise regulatory frameworks and to ensure that progress made through controlling AMR within Europe is not put at risk through importation of resistant bacteria (or determinants) from regions with less rigorous controls.

CVMP's proposed actions:

- The CVMP will continue to seek input from stakeholders (including the pharmaceutical and livestock industries, and veterinary associations) when developing guidance documents and reflection papers.
- We will collaborate with colleagues in **EU agencies** (e.g. EFSA, ECDC) and other **international regulatory bodies** in developing guidance and advice (e.g. OIE, TATFAR and WHO).

Annex

CVMP status report on activities on antimicrobials

Summary

In order to facilitate the development of the new CVMP strategy on antimicrobials for 2016-2020, this Annex on activities on antimicrobials has been prepared as a review of the activities carried out after the adoption of the previous CVMP Strategy on Antimicrobials (2011-2015).

The CVMP strategy 2011-2015 summarised the following areas of activities:

Strategy 2011-2015	**CVMP actions taken**
The CVMP perceives the need for effective antimicrobial treatment for relevant indications in all species.	Revisions to Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/261180/2012) Question and answer on the CVMP guideline on the SPC for antimicrobial products (EMA/CVMP/414812/2011-Rev.1) Question and answer - Suitable pack sizes for antimicrobials (draft under preparation) AMEG answer to Question 3 - Answers to the requests from the European Commission for scientific advice on the impact on public health and animal health of the use of antibiotics in animals (EMA/381884/2014) Revisions to Guideline on the conduct of efficacy studies for intramammary products for use in cattle (CVMP/EWP/141272/2011)
The CVMP wishes to encourage an increased level of innovation on treatment alternatives for infectious diseases.	Scientific advice has been provided on request from MA applicants on the development of new antimicrobial products, and alternatives to antimicrobials. Through Scientific Advice, CVMP has provided guidance on “alternatives” including immunostimulants and vaccine products. The regulatory path for novel products including alternatives to antimicrobials is also supported through the ITF and the CVMP’s ADVENT group. Joint EFSA and EMA scientific opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (ongoing).

Authorised antimicrobials should have product information recommending the products to be used in a responsible way to avoid unnecessary selection pressure for AMR.	Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union (EMA/CVMP/SAGAM/741087/2009) Reflection paper on use of pleuromutilins in food-producing animals in the European Union (EMA/CVMP/AWP/119489/2012) Concept paper on use of broad-spectrum penicillins in animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/37203/2015-Draft1) Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/721118/2014) Use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health (EMA/755938/2012) Use of glycylcyclines in animals in the European Union: development of resistance and possible impact on human and animal health (EMA/291760/2013) CVMP referrals for antimicrobials (e.g. enrofloxacin, 3rd- and 4th-generation cephalosporins, tylosin, colistin and gentamycin)[9]
Protocols for pivotal clinical trials should consider responsible use principles.	Revisions to Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/261180/2012)
Risk mitigation measures at a proportionate level are needed to contain risks for human health.	Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013) AMEG answer to Question 4 - Answers to the requests from the European Commission for scientific advice on the impact on public health and animal health of the use of antibiotics in animals (EMA/381884/2014) Reflection paper on the Risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP/401740/2013)

[9] For further reference see http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_referral_search.jsp&mid=WC0b01ac05805c5170

The need to allow off label use under some circumstances is acknowledged. However such use may constitute a non-assessed risk to public and animal health related to AMR.	Reflection paper on off-label use of antimicrobials in selected domestic animals (draft under preparation at AWP) Reflection paper on meticillin-resistant *Staphylococcus pseudintermedius* (EMEA/CVMP/SAGAM/736964/2009)
The CVMP work should be seen in a context as a part of an overall EU strategy on antimicrobials.	CVMP supports the EMA ESVAC project on monitoring of sales. (EMA/238630/2011, EMA/88728/2012, EMA/236501/2013, EMA/333921/2014) Answers to the requests from the European Commission for scientific advice on the impact on public health and animal health of the use of antibiotics in animals (EMA/363834/2013, EMA/381884/2014) In total the CVMP provided recommendations on 45 referrals encompassing more than 6 classes of antimicrobials and numerous veterinary medicinal products. (Progress report on the Action plan against the rising threats from Antimicrobial Resistance - Annex 2). The CVMP is contributing to the Joint EFSA and EMA scientific opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety Participation at Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) where input is provided by the EMA on the CVMP activities on AMR. Comments provided to the work of international organisations as required (e.g. WHO, OIE, Codex Alimentarius).

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