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4 CVMP strategy on antimicrobials 2011-2015

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Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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CVMP Vision Statement on antimicrobials[1] 2011-2015

The CVMP strategy seeks to promote the continued availability of effective antimicrobials for use in animals whilst at the same time acting to minimise risks to animals or man arising from their use.

To deliver this vision the CVMP will:

- Consider available data on antimicrobial resistance (AMR) and give AMR related risks adequate weight in the benefit risk assessment on which a decision to authorise, or to restrict the use of, an antimicrobial is based. When appropriate, risk mitigation measures will be included within the terms of the authorisation. The CVMP Scientific Advisory Group on Antimicrobials (SAGAM) will be consulted to provide high quality scientific advice coherent with the most recent knowledge.
- Work in collaboration with other interested parties to promote prudent and responsible use of antimicrobials throughout EU in a farm to fork perspective. Approvals of antimicrobials are based on the assumption that they will be used prudently and according to the label and thus for the risk mitigation measures to be effective, it is important that the recommendation given in product literature are fully implemented in everyday veterinary practice.
- Keep updated on the current knowledge on AMR including levels of resistance and volumes of sales of antimicrobials, as well as on methods for collecting and interpreting such information. With assistance from SAGAM, CVMP will publish reflection papers on matters related to AMR and contribute to the work of other expert groups working in this area.
- Provide recommendations on measures to be taken to minimise risks from AMR related to the use of veterinary products when appropriate. On request from the European Commission or member states CVMP will reconsider the terms of authorisation of approved products in the context of referral procedures to ensure that compliance with prudent use principles is applied, updated or maintained.

Summary of the CVMP strategy on antimicrobials 2011-2015

- CVMP perceives the need for effective antimicrobial treatment for relevant indications in all species.
- CVMP wishes to encourage an increased level of innovation on treatment alternatives for infectious diseases.
- Authorised antimicrobials should have product information recommending the products to be used prudently to avoid unnecessary selection pressure for AMR.
- Pivotal clinical trials should be conducted according to prudent use principles.
- Risk mitigation measures at a proportionate level are needed to contain risks for human health.
- 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.
- CVMP work should be seen in a context as a part of an overall EU strategy on antimicrobials.

[1] OIE definition "Antimicrobial agent": *"means a naturally occurring, semi-synthetic or synthetic substance that at in vivo concentrations exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms). Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition"* (http://www.oie.int/eng/normes/mcode/en_glossaire.htm#rubrique_definitions)

Introduction

In this document CVMP presents for the third time its strategy on antimicrobials. The need for comprehensive guidance on how to ensure availability of effective antimicrobials whilst safeguarding against the increased levels of resistance was first discussed in the *Risk Management Strategic Plan for controlling antimicrobial resistance through authorisation of veterinary medicines* adopted in 2000. That document was followed by the *CVMP Strategy on Antimicrobials 2006-2010 and Status Report on Activities on Antimicrobials* where CVMP presented a status report and proposed a number of actions.

The objective of this document is to present the CVMP's view on responsibility with regard to antimicrobial resistance (AMR) covering both animal and public health aspects. CVMP considers it important to update its view on AMR periodically in order to keep aligned with the ever changing animal and public health situation while applying the experience it has gathered from marketing authorisation approval. This includes reflections about usage pattern of antimicrobials in the field and collaboration within and outside the EU in order to make the strategy most effective. Intentions for direct action during the next five year period are added in boxes following each section.

In accordance with Regulation (EC) No 726/2004, the CVMP is responsible for preparing the Agency's opinions on all questions concerning veterinary medicines. With regard to antimicrobials this responsibility includes considerations of risks related to development, emergence and spread of antimicrobial resistance. Such risks may be either risks to animal health due to lack of effective treatment options or risks to public health due to exposure to resistant bacteria (zoonotic or commensal organisms carrying resistance determinants). Exposure could be either through direct contact with the animal, via the environment or via food of animal origin and the level of exposure will be dependent on the selection pressure that unavoidably arises from the use of antimicrobials.

Another possible risk for public health is linked to residues in food. This risk is considered as detailed in the VICH guideline 36 (Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI) and is not further discussed in this document.

The CVMP can act on several levels; marketing authorisations (including wordings in product information), guidance documents and reflection papers. Reflection papers have been used to promote certain risk mitigation measures such as the need to retain some antimicrobials for second line use. CVMP assessment of data provided in support of applications for marketing authorisations constitutes the basis for European Commission decisions. These procedures aim at ensuring that veterinary medicines on the market have a positive benefit-risk balance when used in the animal population they are intended for and this balance includes considerations of risks related to antimicrobial resistance. Risk mitigation measures (including SPC warnings) on a proportionate level are of importance to minimise such risks and thereby increase the lifetime of effective antimicrobials on the market and reduce risks to public health related to spread of drug residues and resistance from animals to humans. Guidance documents on antimicrobial efficacy and antimicrobial resistance provide an important framework for applicants and assessors and reflection papers provide a tool to express the views of CVMP.

Multi-resistant bacteria are an emerging global problem. In the field of veterinary medicine both farm animals and companion animals are affected. The problem cannot be reliably quantified as there is insufficient surveillance data on resistance in animals, but reports on emerging resistance are now common.

During the last decade a number of events have stressed the need for increased awareness of public health aspects related to antimicrobial resistance in animal husbandry. For example, the emergence of ESBLs (extended spectrum beta lactamases including AmpC and carbapenemases) shows that risks to human health include the possibility of horizontal transfer of resistance genes. Thus, foodborne risks

go beyond spread of zoonotic bacteria (such as Salmonella and Campylobacter). In addition, clonal spread of a certain meticillin resistant Staphylococcus aureus (MRSA) strain in livestock represents a risk to human health from contact with animals. This exemplifies that risks for humans related to antimicrobial resistance in animals are not restricted to foodborne risks alone.

1. CVMP perceives the need for effective antimicrobial treatment for relevant indications in all species

When animals are diseased and suffering, there is a need to treat them or to alleviate their pain by other means.

Ideally the prescriber should have several different treatment options available for all infections and all species. CVMP notes that although the number of approved products on the market continues to increase, there are still large gaps in approved indications pertaining to a number of infectious diseases especially in minor species. In many cases these gaps could be filled by adding new species/indications to existing marketing authorisations or by presenting new formulations containing known active substances.

Availability of different formulations of narrow spectrum antimicrobials is of special importance as these are essential to allow targeted treatment. It would be beneficial to increase the number of such products on the market especially products that offer convenient treatment alternatives to make it attractive to tailor treatment based on correct diagnosis.

CVMP would like to encourage initiatives to increase the number of product alternatives on the market covering different species and indications including those with a limited market. A number of national marketing authorisations exist and where appropriate these could be expanded to cover all of the EU provided AMR risks have been adequately assessed and mitigated. CVMP will look favourably upon developments that increase the number of narrow-spectrum antimicrobials especially those formulated to increase compliance and thereby providing practical alternatives to broad spectrum antimicrobials.

2. CVMP wishes to encourage an increased level of innovation on treatment alternatives for infectious diseases

Already today there are certain diseases where treatment outcome is compromised by high resistance levels against most antimicrobials and there will for the future a need for new treatment alternatives, covering both antimicrobials and non-antimicrobial treatments (vaccines etc) against bacterial diseases and diseases that may precipitate secondary bacterial diseases.

When it comes to antimicrobials that offer new treatment options (e.g. due to a new mechanism of action), CVMP sees a potential inbuilt conflict in cases where the same molecule is developed in parallel for both human and veterinary use as the veterinary use of antimicrobials might constitute a risk factor for emergence of resistance in humans. CVMP intends to collaborate closely with the human side and communicate with industry at an early stage to allow specific assessment of such drugs and when appropriate restrict them as last resort medicines for humans. Such restrictions should be made based on risk assessment in each case to allow appropriate decisions without unnecessarily restricting availability on the veterinary side.

CVMP will work to reduce the current perceived risk in developing antimicrobials for veterinary use by clarifying the opportunities and restrictions on development of novel antimicrobials. This would require close collaboration with ECDC together with a dialogue with industry early in product development. Measures to promote scientific advice for AMR issues should be developed. This includes initiatives for non-antimicrobial treatment or prevention against bacterial diseases.

3. Authorised antimicrobials should have product information recommending the products to be used prudently to avoid unnecessary selection pressure for AMR

Prudent use of antimicrobials, as defined e.g. in Chapter 6.9 in the OIE Terrestrial Animal Health Code, is regarded a cornerstone to contain resistance for benefit of both animal and human health.

Within the process of approval of veterinary medicinal products, the summary of product characteristics (SPC) is used as the tool to make available appropriate information in the case of both products approved since long time and new products on the market. To allow users to comply with prudent use principles the SPC should clearly describe the conditions under which the antimicrobial products are to be used.

Indications should be clear and precise. Doses should be optimised to ensure effective therapy without inducing unnecessary emergence of resistance including avoidance of unnecessarily long treatment periods. To enable the users of the product to take an evidence based decision on the correct use of the product in the various field conditions, information on pharmacokinetic/pharmacodynamic properties of the antimicrobial agent, including information on sensitivity of the target pathogens should be presented in line with the requirements of the respective SPC guideline. Preventive treatment of an entire group/flock when infection has started in some animals should be restricted to highly contagious and severe diseases. Oral products for group or flock medication is of special concern since in intensive animal production there might be comprehensive use of antimicrobials and from a pharmacological perspective treatment is not well controlled as the ingested doses varies between animals and the exposure to the GI-tract (where most zoonotic bacteria are present) will be high. In addition, there is pressure for enhanced performance of animals which might imply short term benefits from non-sustainable use of antimicrobials.

Fluoroquinolones and 3rd to 4th generation cephalosporins are second line antimicrobials to be reserved for conditions that have responded poorly or are likely to respond poorly to other classes of antimicrobials and they should not be used for general prophylaxis e.g. in pig and poultry production. More emphasis should be put into promoting this restriction to reserve these critically important antimicrobials for situations where they should be used according to prudent use principles. In this respect, group and flock treatments must be justified in relation to the severity and contagiousness of the disease. Fixed combinations with second line antimicrobials for mass medication are of special concern and thus of high priority for action.

Macrolides comprise an important group for action as low dose/long term treatment is still approved for some products in some countries. From the high number of products available (including numerous products where macrolides are included in fixed combinations with other antimicrobials) and considerable geographical differences, there seems to be room for revisions of the SPCs without compromising availability of effective treatment options.

Pleuromutilins are regarded by CVMP as critically important antimicrobials in veterinary medicine as they are the sole therapy for some conditions such as macrolide resistant infections of *Brachyspira hyodystenteriae* in swine. Therefore the need for avoidance of unnecessary use of pleuromutilins must be stressed.

Following its recommendations on fluoroquinolones and 3rd to 4th generation cephalosporins CVMP has agreed a priority list for action. Warning sentences as recommended have been implemented in SPCs for all fluoroquinolones containing products and similar exercises are recommended for cephalosporins.

The committee notes the need to update SPC texts for numerous products to ensure that texts are balanced and consistent with CVMP recommendations, current state of art and scientific/technical knowledge. Fluoroquinolone containing combination products have highest priority for action using the referral tool. It needs to be assessed whether there are any appropriate indications for fixed combinations with second line antimicrobials. Products for group/flock medication are of special concern.

SPCs for fluoroquinolones and cephalosporins are recommended to be updated to ensure clear and specific indications and appropriate posology. Well established products with sparse documentation and generics of such should not have broader indications or longer treatment periods approved as compared to those which have a complete and/or updated documentation.

CVMP has recently (November 2010) published for consultation recommendations for macrolides[2]. It is anticipated that there is a need for referrals to update the indication and posology sections of some SPCs especially products for group/flock medication.

CVMP together with SAGAM will reflect on the need for action on pleuromutilins.

4. Protocols for pivotal clinical trials should consider prudent use principles

Marketing authorisations are granted with indications for use based on the results from pivotal clinical trials. To allow products to be used prudently in practice it is crucial that such studies are designed in a way that takes into account prudent use principles. There is certain problem areas related to this that needs to be further elaborated on. For instance there might be a need for special study design when documenting effects from antimicrobial classes such as fluoroquinolones and higher generation cephalosporins that are intended to be second line treatments.

In many cases, for instance chronic or mild infections and in all cases of preventive treatment, studies should be designed to allow assessment of rate of self cure as need for antimicrobial treatment might not be obvious. In addition there might be a need to assess the additive effect for antimicrobials compared to non-antimicrobial therapy.

CVMP and its Efficacy Working Party will together with SAGAM further elaborate on requirements for clinical trials and if needed revise the relevant guideline.

[2] Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the EU available at http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500099151

5. Risk mitigation measures at a proportionate level are needed to contain risks for human health

In the EU, the dossier requirements for veterinary medicinal products are laid down in Directive 2001/82/EC, as amended[3], attention should be given to guidance on pre-approval efficacy and post-marketing surveillance. In addition, a guideline (GL27[4]) to detail dossier requirements for approval of veterinary medicinal products for food producing animals with respect to antimicrobial resistance has been developed by VICH with active participation from CVMP. Beyond food-borne risks there will be a need in the future to address risks related to contact between animals (including companion animals and horses) and humans. It is essential that an antimicrobial resistance risk assessment in relation to dossier assessment is made in a structured, consistent and transparent way.

Risks related to AMR are to be considered in the benefit/risk assessment and in case these risks are found unacceptably high and cannot be sufficiently mitigated marketing authorisation will not be granted.

Of special concern are molecules that represent totally new modes of action (and thus resistances unrelated to those already evident on the market) and a very strict view will be applied where the molecules in questions are specifically reserved as last resort medicine for use in zoonotic infections in humans.

CVMP will elaborate on the need for further guidelines and update of existing guidance on AMR risk analysis as related to approval of veterinary medicinal products. Linked to this the committee will elaborate further on specific issues related to benefit/risk assessment of antimicrobials. The CVMP Efficacy Working Party and SAGAM will assist CVMP in this task as appropriate.

Quality assured training of assessors is also considered important.

6. 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

Use of antimicrobials in veterinary medicine is not restricted to use of approved veterinary medicinal products, nor to approved indications, doses or methods of administration. Veterinary medicinal products are used for non approved indication and posologies, tentatively or in cases where there is evidence based data available but where SPCs have not been updated accordingly. In addition there is an established use of medicinal products approved for human use according to "the cascade"[5]. CVMP acknowledges the need of such off label use to ensure availability of medicines needed for animals. However, increased awareness of AMR is needed for such prescription as in those cases the responsibility for AMR risk assessment is placed on the prescribing veterinarian. CVMP sees a need for increased awareness and improved competence among veterinarians to ensure prudent decisions. Of special concern are those molecules that are restricted in the human side to be reserved as last resort medicines. Use of such substances in veterinary medicine should be avoided as far as possible. In case of such life threatening infections where there is a need for treatment with last resort medicines in animals, treatment should always be evidence based and consider risks for selection of resistance.

[3] Directive 2001/82/EC on the Community code relating to veterinary medicinal products, as amended by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004.
[4] VICH GL27: Guidance on the pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004308)
[5] See Article 10 and 11 of the Directive 2001/82, as amended

Off-label use also comprises situations where the practitioner changes the dose or treatment duration of a product authorised for veterinary use from the label recommendation. Further work is needed to consider how CVMP should approach antimicrobial products, which are approved with a dose that has been shown to be too low both in relation to real-life efficacy and resistance development. Such situations are complicated by the fact that simply increasing the dosage will also influence several other factors of the benefit-risk balance, e.g. target animal safety, withdrawal period, environmental risk assessment etc.

For the future it would be appropriate to have a system to restrict "the cascade" in case of risks related to AMR to allow proportionate risk mitigation following appropriate scientific risk analysis. CVMP will work with the European Commission and other stakeholders to define the best way by which such restrictions on off label use might be introduced without inappropriately comprising the clinical freedom of veterinarians.

CVMP has recently presented recommendations on meticillin-resistant *Staphylococcus pseudintermedius* in dogs and the committee is willing to take part in further work to address the issue of AMR related risks from veterinary use of antimicrobials off label and will contribute to any action aiming at increasing the prescriber's awareness.

CVMP will further consider risks related to off-label use when reflecting on efficacy, resistance and benefit-risk for antimicrobials.

7. CVMP work should be seen in a context as a part of an overall EU strategy on antimicrobials

Support to activities aimed at the promotion of prudent use principles is regarded as a cornerstone to contain resistance and these by definition includes activities that involve a number of different players, of which CVMP is only one. The remit of CVMP is to provide scientific opinions as a base for setting MRLs and approving of veterinary medicinal products together with giving scientific advice and guidance in these areas, whereas the total concept of containing antimicrobial resistance is much broader and covers numerous aspects of veterinary medicine and animal husbandry. To play an appropriate part in this context, CVMP is actively involved in the scientific debate on antimicrobials and will have an open dialogue with other parties about the efforts necessary to contain AMR. It is acknowledged that the amount and pattern of use depends on numerous different factors, some of them economic and therefore appropriate product information is not by itself a sufficient measure.

There is an increasing need for collaboration between institutions on AMR. CVMP is today active on a number of different platforms; supporting EMA in several projects, collaborating with other bodies e.g. EFSA, ECDC and the European Commission. Collaboration between national competent authorities and networking of experts is also seen as an important activity.

Over the period covered by this CVMP Strategy, the European Commission will be implementing the revised Community Animal Health Strategy (CAHS) 'Prevention is better than cure'. Antimicrobial resistance is an area that requires a coordinated approach between human and veterinary communities as both animal and human health is dependent on effective means to treat infection diseases. Therefore this CVMP strategy of AMR should be read in conjunction with the Community Animal Health Strategy.

In CVMP's view a global (EU)-strategy on antimicrobial resistance is urgently needed. The management of this problem for society cannot be left 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 it is not a problem that the consumer can solve through the shopping basket.

The following elements are found essential in this EU strategy (the list is not intended to be exhaustive):

- Animal management/husbandry aspects should be included in the discussion as ultimately antimicrobials are not needed when the animals are healthy. 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 individual animal surveillance and treatment using modern electronic techniques are important points to consider. Use of vaccines should be promoted. For some infective diseases where vaccines are on the market, antimicrobials may be easier and cheaper to use.

- Education of veterinarians and farmers and other measures to increase compliance with recommendations given are highly important. Prudent use principles need to be implemented in everyday life at farms and animal clinics.

- A tendency towards increased advertising and a reduction in prices of antimicrobials is noted. The number of approved products has increased considerably during the last 10 years without a corresponding increase in the number of treatment options because new product applications are in many cases products with the same active substance, indications and resistance patterns as already approved products. This intensified competition is likely to lead to an increase of overall use of antimicrobials with corresponding increase in resistance

- Monitoring of data on sales/consumption of antimicrobials is essential. Such monitoring is a prerequisite for the evaluation of the extent to which given recommendations are complied with and of the impact of measures taken to promote prudent use. To allow such impact assessment it is highly important to have available harmonised accurate and detailed data on sales of antimicrobials covering both food producing and companion animals. Preferably it should be possible to collect data on use per species and per indication.

- Monitoring of resistance is of importance to identify areas there might be a need for action. Besides data from surveillance programmes and EU zoonosis reports mapping the prevalence of zoonotic agents and commensals from food producing animals of relevance for human health there is an increased need to monitor target animal pathogens (covering both food producing and companion animals) and to develop harmonised diagnostic tools and interpretation criteria.

To ensure that any future measures to be taken with respect to veterinary use of certain antimicrobials are proportionate and effective, a risk analysis at an appropriate level of detail should be performed in each case according to principles as outlined in the Codex Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, preferably before the action is taken. In this respect, both positive and negative impacts on animal and/or public health should be considered. Further work is needed to quantify the magnitude and impact of the flow of resistant bacteria or resistance determinants from (certain areas of) the veterinary field to the human field.

CVMP will work for an overarching EU-strategy on AMR in veterinary medicine, covering both human and animal health aspects, and supports initiatives to create a common platform for AMR risk management activities including further work on the impact and consequences of veterinary use patterns. This includes communication and collaboration with the Commission, EFSA and ECDC but also different interested parties in animal production. In this work CVMP will be supported by the CVMP Efficacy Working Party and SAGAM as appropriate.

CVMP supports the recently introduced EMA project on monitoring of sales (European Surveillance of Veterinary Antimicrobial Consumption, ESVAC). Once available, CVMP/SAGAM will use data from ESVAC to be used as background information for impact assessment of taken measures.

CVMP supports activities related to monitoring of resistance both the EU zoonosis reports and projects studying target animal pathogens, especially those working for a harmonised methodology and interpretation criteria within the EU and globally.

Annex

CVMP STATUS REPORT ON ACTIVITIES ON ANTIMICROBIALS

SUMMARY

In order to facilitate the development of the new CVMP strategy on antimicrobials for 2011-2015, this CVMP status report on activities on antimicrobials (2010) has been prepared for reviewing the activities carried out after the adoption of the previous CVMP Strategy on Antimicrobials (2006-2010).

REVIEW OF PROGRESS SINCE CVMP STRATEGY ON ANTIMICROBIALS (2006-2010).

The CVMP strategy 2006-2010 summarised the following areas of activities.

Strategy 2006-2010	**CVMP actions taken**
Ensure harmonised interpretation of dossier requirements by efficient training of assessors.	One training of assessors session (*Antimicrobial products: Specific aspects of efficacy and safety assessment*) was held in Dec 2007 and another on assessment on data from VICH GL27 is planned for 2011.
Provide guidance on how to interpret the data requested according to GL27 and when to provide additional information	This work was initiated but later withdrawn. It was concluded that further guidance for industry was not needed and guidance on how to assess data could be given at training sessions.
Develop further guidance for orally administered products. This should also include considerations about the maximum treatment periods and possibilities to further use PK-PD modelling in the establishment of the best dose and dosing regimen.	No guidance documents have been developed. It was concluded that this area needs to be covered on product level rather than generally. A number of referrals have been run during the period where doses and treatment periods have been evaluated.
Consider the available information on antimicrobial resistance in the EU including the data from surveillance programmes and EU zoonosis reports.	Such data have been considered as appropriate in relation to the need for warnings sentences to be put in SPCs e.g. during referrals.
Stress the importance of availability of information on the overall use of antimicrobials from the Member States.	CVMP supports the EMA ESVAC project on monitoring of sales.

Enhance the communication with other parties especially EFSA, ECDC, FVE and veterinary medicines industry in order to more efficiently exchange information on resistance issues and usage of antimicrobials. Active involvement in the scientific debate on antimicrobials to have an open dialogue with other parties about the efforts, which are necessary to maintain the efficacy of antimicrobials.	During the period CVMP has been involved in the Codex Alimentarius TFAMR and together with other bodies participated in the projects Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections (ECDC, EFSA, EMA, SCENIHR) and Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant *Staphylococcus aureus* (MRSA) in livestock, companion animals and food. In addition CVMP/EMA together with HMA and the Czech presidency organised a meeting in Marienbad in May 2009 where interested parties were invited and AMR has been on the agenda at several meetings with interested parties such as at a Focus group meeting on fluoroquinolones in October 2006.
Finalise the review on fluoroquinolones	All proposed warning sentences are now included in SPCs for products of concern. The Commission has invited CVMP to propose further referrals to be made to address issues related to indications and posology. This work has been started.
Initiate activities on other groups of antimicrobials that are listed as critically important for human use, in particular 3rd and 4th generation cephalosporins.	A reflection paper with recommendations on cephalosporins was published in 2009. The work with the implementation of those recommendations is to be started. Referral procedures similar to those on fluoroquinolones will be needed.
Take further initiative and explore possibilities to liaise with the regulatory authorities outside the EU, in particular those of the United States and Japan, on antimicrobial issues.	CVMP supports increased collaboration between FDA and EMA and notes that these two bodies have a confidentiality agreement and exchange information on AMR on a regular basis.

It is concluded that the CVMP has made substantial efforts in the field of AMR over the last 5 years. The work has been ongoing, in general successfully, and most of the goals as detailed in the strategic plan for 2006-2010 have been achieved. However, during this period AMR related issues have become increasingly important and in many cases actions taken during this period represent initiatives that need to be continued and expanded.