HMA-V Action plan on antimicrobial issues

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1. Introduction

Antimicrobial resistance (AMR) is considered to be a major global public health concern and a potential food safety issue. In the area of veterinary medicine, this issue needs to be considered both from a human health perspective and from the perspective of protection of animal health and welfare and the environment.

Resistance in bacterial species can cause difficulties in the treatment of both the life threatening and serious, injurious infections in humans and animals.

This leads to concerns about a number of important impacts in the area of public health, medical care, financial resources and others.

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In view of the increasing trend in multidrug-resistant bacterial infections in both man and animals, the lack of development of new antimicrobials in the human and veterinary field is of great concern. The availability of new antimicrobials for use in humans and/or animals is limited and only a few classes of antimicrobials have been developed in the last 30 years (fluoroquinolones, lipopetides and oxazolidinones). The other recently released antimicrobials declared as new classes (ketolides and tigecycline), are related to the existing classes (macrolides and tetracyclines), so they should rather be regarded as new generations of the same group. The reasons for the situation are complex and as such, the situation needs multifaceted and comprehensive solutions.

The increasing concerns related to AMR led to various actions at the level of scientific, regulatory and political bodies both in the EU and worldwide.

In the EU, at the 2876th meeting of the Employment, Social Policy, Health and Consumer affairs Council, conclusions (Press No. 9637/08) have been adopted which constitute a framework and give a high political profile regarding further steps that are to be taken with respect to AMR in the EU in both human and veterinary medicine.

At present, activities in the area are ongoing in the EU, initiated by different bodies such as HMA, the NCAs and the European Commission with advice from its agencies (e.g. the European Medicines Agency). There is a need to coordinate these activities to allow close collaboration and efficient use of resources between all EU bodies that share part of the responsibility and harmonisation of eventual outcomes. As an active network, HMA has a clear role in facilitating and harmonising the implementation of agreed measures taken to reduce the risks at a national level. The goal is to reduce risks primarily for human health, but also for animal health, without reducing the availability of therapeutic choices for veterinary medicines in a disproportionate manner. Activities to promote responsible use of antimicrobials are currently deemed one of the most important and effective means to reach this goal.

2. HMA strategic plan on antimicrobial issues

The concerns related to AMR have been discussed by the HMA as a result of which a strategic plan was prepared on veterinary medicine related antimicrobial issues. The objective for this strategic plan is to identify areas where HMA has responsibility to catalyse, facilitate and directly implement activities within the EU and identify those areas where involvement of HMA with other parties would be beneficial.

The HMA strategic plan on antimicrobial issues provides the HMA with a vision with respect to AMR. In addition to the HMA vision, the HMA Strategic plan defines the relative responsibilities of both National Competent Authorities (NCAs) and of HMA acting collectively. Concrete steps/actions to be taken by the HMA and NCAs are outlined in the HMA action plan.

3. HMA Action plan on antimicrobial issues

HMA and NCAs are expected to initiate all appropriate actions to identify and, where appropriate, catalyse ongoing activities within the EU to make it possible to take appropriate risk management measures in line with evidence-based principles in order to ensure that the measures taken are balanced and that they reflect the real risk(s). Such actions may be

- identification of the areas/issues which need to be addressed,
- provision of data in different defined areas,
- sharing experience,
- active implementation of agreed actions.

It is therefore expected that the HMA will identify areas of interest and, within the framework of such areas, will take concrete actions with clear responsibilities and timeframes (section 3.1). It is equally important that the respective, responsible bodies in addition to the HMA, are identified in order to map activities/responsibilities (section 3.2). Actions may need to be assigned different priorities and they may need different preparatory periods/discussions with stakeholders before they are taken forward.

Where applicable, actions are ranked as

- short term – to be implemented within the period of approximately 1 year,
- medium term – to be implemented within the period of approximately 3 years and
- long term - to be implemented beyond the 3 years period.

3.1 Definition of the areas for further steps (direct actions at HMA level):

Description	Time frame/HMA action
1. Communication strategy for interaction with stakeholders in the Member States and at the Community level	
Responsibilities of NCAs and other bodies concerned might overlap as for example with food, agricultural and/or environmental agencies. A "communication pack" may assist NCAs to implement effective communication with those bodies. In addition HMA may need to identify the stakeholders (e.g. EC, EMA, OIE, CVOs, EFSA, IFAH, FVE, farmers, consumers, etc.) to be covered by the communication strategy and the way of communication.	1) To map out all of the stakeholders in the areas of antimicrobials. (short term) 2) To develop a communication pack on the issue of antimicrobial resistance and the prudent[1] use of antimicrobials. (short term)

[1] "Prudent use of antimicrobials", for the purpose of this document is synonymous with "responsible use of antimicrobials". It does not simply mean using less antimicrobials, it means justified use (based on a properly established diagnosis) of the most appropriate sensitive antimicrobial in a way optimising its clinical efficacy in the specific clinical cases and taking reasonable steps to ensure the method of use (including dose regime) and precautions applied help limit the potential for resistance to develop.

2. Legal classification of antimicrobial VMPs	
All antimicrobial VMPs shall be classified as prescription only medicines. This category may be further divided into sub-categories in accordance with the MS´ legislation to consider also companion animals.	1) The HMA shall make a survey on the prescription status of antimicrobial VMPs in the EU/EEA (short term) **Complete and findings circulated to relevant groups** 2) The results from the survey will be fed into the discussions of the HMA Working Group considering the future EU legislation and also the ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) project. (medium term)
<u>3. Mapping of prescription and use habits</u>	
The knowledge about habits for prescription and use of antimicrobials in EU is sparse. It is important to gain more information on compliance with existing prudent use guidelines such as the Codex code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005) and OIE Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine. In addition, information on current prescription and use habits is needed as a baseline against which the effectiveness of possible actions to change those habits could be measured, e.g. impact assessment of SPC warnings.	1) Network to establish the extent to which different MS can access information on prescription and use habits. (short term) 2) Develop a strategy on how best to promote appropriate prescribing practices by veterinarians as part of prudent uses. (medium term)

3.2 Identification of other areas where HMA has a responsibility to facilitate collaboration and implementation of action to be taken

Responsible body / Description	Time frame / HMA action
1. Monitoring of sales of antimicrobial VMPs	
EMA has accepted the task to collect data for monitoring of sales data for antimicrobials for veterinary use. This work is initiated and as a first step the criteria and a template for the collection of data to ensure that data are presented in the same way in all member states has been provided. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project follows a stepwise approach pending resources for implementation at EMA and Member State level and all sales of all antimicrobial agents are to be included. Data are currently being collected from 10 Member States in a harmonised manner as part of a pilot project and some other Member States are starting to collect data according to the EMA agreed data collection form. The project envisages migrating from monitoring sales to monitoring actual use (species, condition, treatment).	1) HMA to coordinate and promote activities at Member State level to facilitate the process to provide data to EMA on antimicrobial sales, and to express support for the project and expectation of future funding. (immediate) 2) HMA to explore whether monitoring of actual use is viable. (long term) 3) HMA to influence the development of an appropriate legal base to enable the provision of relevant information on sales and if appropriate use of antimicrobials.
2. Monitoring of resistance in zoonotic and indicator bacteria	
There is a zoonosis monitoring programme co-ordinated by **EFSA** implemented in the EU. In addition, there are other programmes established in the **Member States** in which data are collected on resistance prevalence (pattern) in	1) The HMA should promote the development of meaningful surveillance programmes that are co-ordinated and use the same principles for data capture, in order to allow meta-analysis of the data. (long term) 2) HMA should work to facilitate the spread of relevant surveillance data between member states and help make this available to prescribers. (medium term)

different groups of microorganisms (zoonotic agents, indicator / commensal microorganisms). These may be official programmes and/or programmes organised by different official/scientific/industry bodies in the Member States.	
3. Monitoring of resistance in target animal pathogens	
As at August 2010, there are no coordinated activities on collection of data for target animal pathogens at EU level. There are national programmes established in some **Member States** in which data are collected on resistance prevalence (pattern) in different target animal pathogens.	1) Despite the lack of funding in this area and the challenges posed the HMA should promote the development of meaningful surveillance programmes that are co-ordinated and use the same principles for data capture, in order to allow meta-analysis of the data. (long term) 2) HMA should work to facilitate the spread of relevant surveillance data between member states and help make this available to prescribers. (medium term)
4. Revision of the SPC of VMPs following CVMP/CMDv recommendations	
A referral at **EMA** to revise the SPCs for (fluoro)quinolones to include warning sentences initiated by EC was finalised in 2010. In addition, further proposals for updating the SPCs for other antimicrobial classes considered critically important in human medicine may follow, starting with the inclusion of warning sentences in the SPC of cephalosporins and continuing with macrolides. Lessons learnt from the (fluoro)quinolones and other AM-related referrals should be applied either to reduce the need for referrals or otherwise to improve the administrative efficiency of implementing prudent use warnings for critically important antimicrobials (e.g. greater use of voluntary measures, effective data provision on concerned products etc.)	1) HMA to promote the work on national implementation of recommendations given by the CVMP and CMDv, and decisions issued by the Commission. HMA should ensure that where through formal harmonisation (i.e. legal base such as article 34 referral) or voluntary harmonisation (e.g. through the CMDv voluntary harmonisation process) changes to the SPC of antimicrobial products are agreed, every MS implements these for all relevant products (short term) 2) HMA to commit resource to voluntary and formal harmonisation aimed at introducing measures to encourage responsible use of antimicrobials taking into account for example the CVMP list of proposed referrals for fluoro(quinolones) (medium term)

5. Harmonisation of SPCs of VMPs	
The same products may be authorised under different conditions within the EU. Such differences include indications, dosage, dosing intervals and other essential features which may influence the proper use of the products - in relation to their effective and safe use. **CMDv** has initiated a voluntary project to harmonise SPCs in different member states. Antimicrobials are among the products to be considered in this project and antimicrobials for food producing species are considered to be the highest priority.	1) HMA to support, through promotion and practical assistance, the CMDv informal harmonisation of SPC scheme for antimicrobial products. (short term) 2) HMA/NCAs to support CMDv in identifying phrases in existing SPCs for antimicrobial products which cause problems, for example conflicting with the principles of prudent use or which are impractical. On the basis of this work, review and propose changes, if appropriate, to the existing CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005). (medium term) 3) HMA/NCAs to support CMDv to seek to agree that informally harmonised SPCs must remain harmonised, with no individual national variations to the SPC being progressed. (short term) 4) HMA/NCAs to support CMDv to develop a strategy on how to deal with nationally authorised antimicrobials with divergent SPCs (species, indications, posology etc). (short term)
6. Communications and training on antimicrobials	
Training of the veterinary health professionals and other users of antimicrobial VMPs is felt to be one of the most effective ways leading to improvement of prudent use of antimicrobials. This is a joint responsibility for **numerous stakeholders** including regulatory bodies, industry, professional associations, academia, farmers' organisations etc.	1) As part of an overall communication strategy, HMA will consider the most effective way that information can be disseminated and communicated to the prescribers/users of veterinary antimicrobials as well as the staff of the EU network. Communication and training should place a strong emphasis on the prudent use of antibiotics[1]. (medium term)

7. EC initiative to contain antimicrobial resistance	
The **European Commission** initiated risk analysis activities by giving a mandate to ECDC, EFSA, EMA and SCENIHR to draft a short report on antimicrobial resistance as related to zoonotic infections. The report has been published; Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections (http://www.ema.europa.eu/pdfs/vet/sagam/44725909en.pdf). The Commission published a "consultation on a staff working paper on antimicrobial resistance", on which a summary of the comments received has been published.[2]	1) HMA to consider the value of the conclusions from the Commission report when considering the benefit risk assessment for market authorisations for veterinary antimicrobials and with respect to activities on antimicrobial resistance in general. (medium term) 2) HMA should take all possible opportunities to contribute to the development and implementation of a European Union strategy for antimicrobial resistance related to veterinary medicines. (Appropriate forums for input include the Presidency, Council and interactions with EMA, EFSA and ECDC.) (medium term)
8. Codex Alimentarius TFAMR	
The taskforce on antimicrobial resistance within **Codex Alimentarius,** hosted by the Republic of Korea, has completed its mandate. The taskforce has created guidelines for the risk analysis process with regard to foodborne issues. The final report is due to be adopted by Codex in 2011.	1) HMA consider the value of and as appropriate take account and contribute to the implementation of Codex recommendations as set out in the taskforce paper issuing of this task force (on-going action)

2 http://ec.europa.eu/food/food/biosafety/antimicrobial_resistance/docs/sum_comments_public_consultation_swp_AMR_en.pdf

9. EMEA/CVMP/SAGAM activities	
The Scientific Advisory Group on Antimicrobials has produced reflection papers on fluoroquinolones, cephalosporins and MRSA which have been published together with recommendations from **CVMP**. A reflection paper on macrolides, lincosamides and streptogramins is out for consultation until 28 February 2011[3] . Recommendations comprise specific actions with respect to prudent use of these critically important antimicrobials The CVMP has published a strategy on antimicrobials 2011- 2015 for consultation until 31 March 2011[4].	1) HMA should co-ordinate activities with EMA/CVMP regarding his HMA action plan with the CVMP 2011 – 2015 strategy. (continuing action)
10. Joint EFSA/EMA/ECDC activities	
EFSA (Biohaz) and **EMA (CVMP/SAGAM)** have together published an umbrella document on MRSA summarising the recommendations from both bodies. The general conclusion is to work for a reduction in the total need for antimicrobials. In addition, the possibility of reserving certain antimicrobials for human use is discussed.	No specific action needed from HMA at this point in time as the recommendations are in line with other agreed HMA activities. However, HMA continue to monitor future joint EFSA/EMA/ECDC activities.

[3] See http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500099151
[4] See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/01/WC500100649.pdf

11. Advertisements	
Conditions for advertisement for VMPs may differ in different Member States as the interpretation of the term 'general public', as provided for in Article 85 of Directive 2001/82, as amended, may differ between Member States leading to divergent practices e.g. regarding who is included in the expression "professional" (prescribers only or also pharmacists and farmers). There might also be a need to request text from responsible use guidelines to appear in advertisements.	1) HMA members to consider, and take action as required (by influencing the content of the revised veterinary EU legislation), if a need is identified to tighten controls on advertising in line with prudent use recommendations. (long term)
12. Restriction of the use of certain molecules	
The possibility to restrict the off label use of certain antimicrobials has been discussed e.g. (i) in relation to the off label use of critically important 'human' antimicrobials for the treatment of multi-resistant staphylococcus in animals. (ii) an increase in the incidence of resistance in certain zoonotic organisms isolated from poultry in some Member States has raised concern on the use of cephalosporins in poultry (*in ovo* or in 1 day old chicks). Measures to control such off label use are currently being considered. This topic is to be addressed during the coming review of the veterinary medicinal legislation with a view to proposing additional legal powers if required.	1) HMA to discuss national experience on use of antimicrobials and the success of measures to decrease unnecessary use of antimicrobials.(short term) 2) HMA to share experience on off label use and the measures taken to control such use with a view to HMA coordinating action at national level in view of the ability of resistant organisms readily to cross borders due to the open market in animals and foodstuffs. (medium term) 3) HMA to influence the future EU legislation so that evidence based controls which have shown to slow the development of resistance are introduced without compromising animal health and welfare. (long term)

13. Research	
Based on different reports published by the EMA, EFSA and other EU bodies, it is clear that the amount of scientific data available on certain key issues is insufficient at the present time. This leads to the situation where the relevant risk assessment cannot be completed and subsequent risk management measures must rely on data which lack the required depth of detail. This topic is to be addressed continuously by different bodies in academia.	1) HMA to support ETPGAH (European Technology Platform for Global Animal Health) discussions on antimicrobial resistance (EMIDA – topic 2) (continuing action) 2) HMA to encourage the co-ordination of existing NCA research programmes on antimicrobial resistance. (medium term)
14. Medicated feedingstuffs	
The impending **review of the feedingstuffs legislation** provides an opportunity to explore the controls for feeds (including liquid feeds) medicated with antibiotics.	1) HMA to ensure appropriate input into the review of legislation. (medium term) 2) HMA to seek regular updates from the Commission on the progress of the review of this legislation. (short term)
15. Economical drivers for prescription pattern	
Breaking the link between prescribing and profit has been found by some Member States to be an effective measure in the context of promoting prudent use Some Member States already have national legislation restricting veterinarians' right to sell antimicrobials or by other means gain economic benefit from prescriptions for antimicrobials.	See 12 above (restrictions improvement of legislation). Also: 1) HMA to consider ways to promote the message that husbandry measures and use of vaccines can reduce the need for antimicrobials leading to longer term economic savings for animal owners. 2) HMA to ensure any new control are proportionate to avoid creating a significant black market for antimicrobials.

16. Authorisation Process	
There are instances where the current authorisation process has resulted in decisions that do not encourage responsible use of antimicrobials. For example, withdrawal periods for some modern antibiotics can make it more economically attractive to use the very antibiotics for which we are trying to limit veterinary use. Allowing more factors to be taken into account when authorising a product in the future may need to be considered. This topic is to be addressed during the coming review of the veterinary medicinal legislation (Directive 2001/82) as amended.	1) HMA to provide appropriate input into the review of EU legislation. (long term)