“One Health”: The Regulation and Consumption of Antimicrobials for Animal Use in the EU

Introduction
Antimicrobials can be considered as ‘societal’ drugs, since any use of an antibiotic, whether in man or animals, has the potential to select for resistance to the antibiotic used. For this reason, much emphasis is now placed on the “One Health” approach to combatting antimicrobial resistance (AMR). In this approach “health” is considered in a global context, including human and animal health as well as the environment. Tackling antimicrobial resistance has recently become a global priority for governments and non-governmental organisations in the healthcare sector from, among others, the European Union (EU) and its Member States, the United States, the World Health Organisation (WHO), the Food and Agriculture Organisation (FAO) and the International Office of Animal Health (OIE). For all of these bodies, AMR continues to rise up the political agenda, reinforced by a renewed interest in the media stimulated by news of “superbugs”, especially those that might result in the death of human patients. The increase in multi-drug-resistant (MDR) infections in man (e.g. Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae), the finding of livestock-associated methicillin-resistant Staphylococcus aureus (MRSA) in man, increased reporting of E. coli extended-spectrum beta-lactamases and carbapenem-resistant bacteria in food-producing animals, combined with the lack of new antimicrobials to cure multi-drug-resistant infections in humans – especially infections caused by Gram negative bacteria – might have a serious impact on the options available to cure not only humans but also animals.

The European Commission’s action plan against the rising threats from antimicrobial resistance aims to coordinate and strengthen all the activities intending to reduce the threat to human and animal health from the use of antimicrobials in human and veterinary medicine within the EU. The action plan identifies key areas for actions to limit the impact of AMR, which are: appropriate use of antimicrobials, prevention of microbial infections and their spread, development of new effective antimicrobials or alternatives for treatment, and cooperation with international partners. Other actions include monitoring and surveillance of antimicrobial consumption and resistance, research, innovation, communication, education and training. Some of these actions have been mandated to the European Medicines Agency (EMA).

This article focuses on those actions within the plan that relate to regulation of antimicrobials for use in animals and illustrates how the One Health approach is applied in practice by the EMA, as well as on other international activities on AMR in which the Agency is involved.

EMA/CVMP Recommendations on Appropriate Use of Antimicrobials and AMR
The summary of product characteristics (SPCs) is a document that describes the properties of a medicine and how it should be used. SPCs may contain risk management recommendations that reflect the risk assessment made during the authorisation process; phrases like “The <antimicrobial> should be used for treatment of severe infections only” are often included in the authorisation of antimicrobials for animal use. Within the EU/EEA, responsible use recommendations, such as those included in SPCs, remain the main risk management tool to reduce the risk of AMR in that they provide users with the essential information that they need to know in order to use the antimicrobial in a responsible and prudent way. For certain groups of antimicrobials, hazard characterisations have been produced by the EMA/CVMP with the support of its experts. Of particular importance are the recommendations relating to 3rd. and 4th-generation cephalosporins and fluoroquinolones which resulted in the European Commission issuing opinions requiring Member States (MSs) to restrict the indications for these products. Further information on these recommendations can be found on the EMA web pages (http://www.ema.europa.eu). The development of resistance mechanisms (acquired or intrinsic) is a dynamic process that can change with time. As a result, the benefit-risk balance of authorised AMs might need to be revisited, depending on information that becomes available on the development of resistance. The importance of an antimicrobial might also change with time, especially in cases where an antimicrobial becomes a last resort choice for human use (e.g. colistin). If required, a Member State or the European Commission might initiate a referral to update and harmonise the conditions of use of existing products, thereby strengthening the responsible use by including updated recommendations in the labelling. The EC has produced draft guidance with recommendations on responsible use of antimicrobials, including a list of actions that have been taken to promote responsible use by MSs. The aim of the guidance is to provide a toolbox with possible actions that may be used to define and promote prudent use. The guidance is expected to be published shortly.

The EMA, following a request from the EC, has recently published scientific advice categorising antimicrobials used in veterinary medicine into the three following categories:

• Category 1; antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited. Includes some classes of antimicrobials that are listed as CIAs by WHO and for which use in veterinary medicine is extensive. Substances like certain penicillins, macrolides, tetracyclines and polymyxins are included in this lower-risk category. When prescribing these...
antimicrobials, the principles of responsible use should be followed.

• Category 2; antimicrobials used in veterinary medicine where the risk for public health is estimated as higher. Includes those antimicrobial classes listed as CIAs by WHO for which the risk to public health from veterinary use is only considered acceptable provided that specific restrictions are placed on their use (i.e. fluoroquinolones and systemically administered (parenteral and oral), 3rd, and 4th-generation cephalosporins). These reserved antimicrobials should only be used when there are no alternative antimicrobials authorised for the respective target species and indication. Two other classes of antimicrobials have been included in Category 2; some penicillins and aminoglycosides for which a hazard characterisation is ongoing.

• Category 3; antimicrobials not approved for use in veterinary medicine. These substances may only be used by way of exception and only in companion animals. This category includes classes of antimicrobials like carbapenems, cyclic esters, glycopeptides or monobactams.

A full list of the substances in each category is available in the advice. One of the recommendations on the advice is to reduce the overall consumption of all antimicrobials (not only of those that are critically important) as any use of antimicrobials might result in co-selection of resistant bacteria. Reduction of consumption of antimicrobials in the EU is one of the key actions of the EC action plan on AMR. Some countries (e.g. Denmark, France and the Netherlands) have successfully implemented programmes to reduce overall antimicrobial consumption. Responsible use of antimicrobials will continue to be the most important objective, and to achieve the desired outcome of controlling AMR, the recommendations on the use of antimicrobials need to be actively implemented by all those responsible for regulating, prescribing and using antimicrobials.

Are New Antimicrobials for Use in Veterinary Medicine Required?

During the last years, few new antimicrobial substances have been authorised for animal use (mostly macrolides and pleuromutilins), none of them belonging to a new class of antimicrobials with a new mechanism of action. The EC action plan on AMR has as one of the key actions the development of new antimicrobials for human use; the action for antimicrobials for animal use is to analyse the need for new antimicrobials.

The EMA scientific advice mentioned above addresses the need for new antimicrobials in veterinary medicine. It concludes that the authorisation of completely new classes of antimicrobials for use in animals might decrease animal and public health risk related to antimicrobial resistance provided co-selection by earlier authorised products is not implicated. To provide certainty on the regulatory requirements for new antimicrobials an early hazard characterisation addressing the risk to public health from AMR is proposed. In addition, there is a suggestion to have in place plans to monitor susceptibility in zoonotic and indicator bacteria in animals for new antimicrobials.

The EMA scientific advice does not indicate any specific therapeutic area for which new antimicrobials are required in veterinary medicine, but provides a description of off-label use of antimicrobials that suggests there is a need for new antimicrobials, or extensions to the indications of existing antimicrobials, in certain specific areas. Market conditions are not currently favourable to the development of new antimicrobials, the reasons for which are, amongst others, the uncertainty of the outcome of applications for marketing authorisation for new antimicrobials. The EMA scientific advice aims to provide some clarity by making proposals on early hazard assessment as well as providing a categorisation of CIAs as described above. The EMA/CVMP is currently developing a 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. This guidance is expected to be released for consultation shortly and will provide further clarification on the requirements for new antimicrobials for animals. More research is now directed to alternatives to antimicrobials; these alternatives can be based on immunological, biological or pharmaceutical active substances. The main limitations on these alternatives are that in most cases they must be used prophylactically. In the case of vaccines, these provide protection against a small number of specific infectious organisms at a time. Other alternative approaches include, among others, the stimulation of non-specific immunity, manipulation of the host microbiome, and the use of bacteriophages, phytonutrients or heavy metals.

Inter-institutional Collaboration on AMR at EU and Global Levels

In line with the One Health approach, a more integrated approach to the problem of AMR is being implemented in the EMA activities on AMR. The EMA advice to the EC has been prepared in collaboration with experts from other EU institutions (the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC)). The first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of AMR in bacteria from humans and food-producing animals, has been prepared together by EMA, EFSA and ECDC. It analyses in detail resistance and consumption from the human and veterinary areas in a comprehensive manner, providing an analysis of possible associations between consumption and resistance. In this report the caveats for such analyses are identified, as well as the areas for improvement.

Cooperation at an international, and indeed a global, level is necessary if AMR is to be tackled effectively. This is exemplified in the range of international activities in which the EMA, either directly or through the European Commission, is involved. At a global level, the WHO is expected to publish a global action plan on AMR in 2015 to which the European Commission has contributed. The EMA also participate in the WHO Advisory Group on Integrated
Surveillance of Antimicrobial Resistance (AGISAR) meetings, and as a member of the ad hoc OIE working group on collecting antimicrobial consumption data in animals which aims to put in place systems for collection of data on use at a global level. The CODEX has produced guidelines for risk analysis of food-borne antimicrobial resistance to which the EU contributed. On a bilateral basis, the EMA is part of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR), which was created in 2009 with the goal of improving cooperation between the US and the EU in three key areas: (1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, (2) prevention of healthcare- and community-associated drug-resistant infections, and (3) strategies for improving the pipeline of new antimicrobial drugs for use in human medicine.

**Surveillance of Antimicrobial Consumption**

Since 2009, the EMA, through its ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) project has been collecting data from the EU and the European Economic Area (EEA) on sales of veterinary antimicrobials. Sales of antimicrobials provide a proxy for exposure of animals to antimicrobials. The data allows analysis of trends in sales of antimicrobials per class in detail. The latest ESVAC report; “Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012”, contains a comparison of the sales from 20 countries for the years 2010 to 2012. A decrease of circa 15% of the sales of antimicrobials (in weight) is reported by these 20 countries, while the animal biomass was stable during this period. The report includes explanations from the ESVAC national contact points on the possible reasons for reduction. The reduction is attributed, amongst other reasons, to the many actions taken by the countries on reducing the overall consumption of antimicrobials in animals, including responsible use campaigns and by setting targets of overall reduction of antimicrobial consumption. Whilst this observation is encouraging, it will be important to continue to analyse sales on an annual basis to confirm that this represents a genuine trend and not merely a fluctuation in sales. In the ESVAC project, the indicator applied to report the consumption of antimicrobials in animals is the amount sold (in weight of active ingredients) normalised by a “population correction unit” (PCU). The resulting measure is mgs per PCU. To take into account the dosing of antimicrobials, a more refined measure than the mg/PCUs is required. The Agency is currently in the process of publishing principles on how to establish more refined units of measurement like defined daily doses and defined course doses as well as starting pilot projects to collect harmonised data on consumption from pig, broiler and cattle farms.

Surveillance data are essential to provide a baseline against which success (or failure) of policies can be measured. Data on consumption of antimicrobials and resistance is a powerful tool that can be used as one of the drivers for risk assessment and risk management.

**Conclusions**

Adopting a One Health approach is necessary for regulating the use of antimicrobials in veterinary medicine in a balanced and proportionate way, so as to retain an adequate range of antimicrobials that can be used to treat infectious disease in animals, bearing in mind that healthy food comes from healthy animals. An international coordinated effort on responsible use of antimicrobials is necessary. There are no borders for resistant bacteria; as a result, measures applied on responsible use of antimicrobials in animals and humans in the EU/EEA should also be applied outside the EU. Development of new antimicrobials for animal use can be useful to decrease antimicrobial resistance; however the risk for public health has to be carefully considered during the authorisation assessment. An early identification of the risks for public health is proposed in order to decrease uncertainties related to the regulatory process. The EU is taking the issue of AMR as one of its priority subjects, and there are early signs that some of the policies and approaches are starting to have a measureable effect. However it is too early to be complacent and much more needs to be done if antimicrobials are to remain widely available for use in animals.

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**References**


**Jordi Torren Edo** works as a Scientific Administrator at the European Medicines Agency (EMA), in the area of safety of veterinary medicines (Animal and Public Health). At the Agency he coordinates activities related to antimicrobials for animal use. He also manages the programme European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), which collects data on sales and use of antimicrobials for animals in the EU. He is a member of the European Commission Working Group on Antimicrobial Resistance that has drafted guidelines for the prudent use of antimicrobials.

**Kari Grave** works as a national expert at the Veterinary Medicines Division of the European Medicines Agency, coordinating the ESVAC project.

**David Mackay** is the Head of the Veterinary Medicines Division of the European Medicines Agency. He acts as the EMA coordinator for those activities of the EMA related to antimicrobial resistance where a One Health approach is required, and represents the Agency within the Transatlantic Task Force on Antimicrobial Resistance.