10 January 2013
EMA/CVMP/680258/2012
Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for a guideline on antimicrobial resistance risk assessment

Agreed by Committee for Medicinal Products for Veterinary Use (CVMP) ad hoc drafting group	19 December 2012
Adopted by CVMP for release for consultation	10 January 2013
Start of public consultation	18 January 2013
End of consultation (deadline for comments)	30 April 2013

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

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1. Introduction

Antimicrobial[1] resistance (AMR) is an important issue to be addressed in applications for marketing authorisations of veterinary medicinal products (VMP). When related to target animal pathogens and possible lack of efficacy, resistance related issues are discussed in the clinical part of the dossier. In addition, risks to public health linked to use of VMP are to be considered and this will include not only risks from antimicrobial residues but also risks from resistant bacteria in food as detailed in Annex 1 to Directive 2001/82/EC as amended. Human beings might be exposed to resistant bacteria either by direct contact with animals or indirectly via food or the surrounding environment. Of the possible exposure scenarios, foodborne exposure (consumers' safety aspects) is the most important to consider due to the high number of people concerned. Foodborne hazards are discussed in the VICH guideline 27 (GL27) (1), which summarises the data requirements for identification of the relevant hazards (foodborne bacteria, either pathogens or commensals, which carry resistance genes). In addition, a brief summary of possible data sources for the exposure assessment is given. However, the guideline does not give any recommendations on how to assess the data. The need for guidance on risk assessment to supplement GL27 has been discussed in the EU for several years. The FDA guideline 152 (Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern) (2) from 2003 was noted and in 2005 CVMP published for consultation a concept paper for further guidance on interpretation of the data from GL27 (3). However, following responses received during the public consultation and further internal discussions it was decided to wait and gain more experience with the use of GL27 before any further guidance was drafted.

Besides foodborne risks there are also potential non-food risks to public health linked to use of antimicrobials in animals including companion animals. One example would be meticillin-resistant *Staphylococcus aureus* (MRSA) which is a zoonosis that may spread via direct contact between animals and humans. Thus, there is a need to discuss the need for risk assessment guidance beyond the foodborne risks discussed in GL27. Another exposure route which may be of high importance is related to the presence of resistant bacteria/resistance genes in the surrounding environment. This area is novel and very little is known about what are the major risks linked to this route of exposure. Although there might be a need to explore this area in the future, today it is likely too early to include such elements in any risk assessment guideline.

The number of new antimicrobial agents on the European market has been limited during recent years and no new classes of antimicrobials have been approved since GL27 came into effect. Applications have been received mainly for new antimicrobial agents within existing classes or for new formulations with known active compounds. Thus only basic data has been provided and abbreviated assessments have been performed. In case of generic applications, no new risk assessments have been performed as the risks related to generics have by default been regarded similar to the risk level estimated for their respective reference product.

The new antimicrobial agents authorised in the EU since 2004 belong mainly to the three groups of critically important antimicrobials listed by WHO as highest priority for risk analysis due to their dual importance in both human and veterinary medicines (4). For these three groups (i.e. fluoroquinolones, 3rd and 4th generation cephalosporins and macrolides) the CVMP has published recommendations based on risk profiles provided by the CVMP Scientific Advisory Group on Antimicrobials (SAGAM)[2]. If

1 Defined according to the 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). In the context of this concept paper "antimicrobial" is most often used as a synonym to "antibacterial".

2 Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000384.jsp&mid=WC0b01ac058002dd37#Antimicrobials

available at the date of submission, these risk profiles have been considered in the AMR risk assessment for the product under application in addition to VICH GL27 data.

Although the experience from VICH GL27 is still limited, a harmonised assessment approach is necessary and therefore CVMP has considered that it is time to progress with a guideline on AMR risk assessment. The aim is to ensure transparency and consistency in decisions by providing a structured assessment model which could be applied by both industry and authorities.

2. Problem statement

AMR risk assessment in the context of marketing authorisation applications for veterinary medicinal products involves several complicating factors:

1) The hazard is not the antimicrobial substance itself but a consequence of its use and the use of the VMP is one of several risk factors. Although use of antimicrobials is regarded a very important risk factor it is nevertheless the case that there are other risk factors determining the risk to public health, e.g. livestock trade and poor hygiene which will increase spread of resistant bacteria between animals, and slaughter house practices which will have impact on the risk for further spread to humans.

2) The hazard identification as described in GL27 considers the resistant bacteria and resistance genes but does not take into consideration the consequences on human health such as severity of the resulting disease and availability of alternative treatments (the “hazard characterisation”).

3) The risk cannot be fully quantified:

   The AMR related public health risks linked to the use of a certain VMP will be semi-quantifiable at best. The number of resistant bacteria will vary depending on what other risk factors are present. Furthermore, there is no parallel to the ADI-concept. It will not be possible to establish thresholds defining a certain “safe level” of resistant bacteria in the gastrointestinal tract.

4) It is not only de-novo development of resistance which is to be considered but also the amplification and spread of strains pre-existing before administration. Thus, the exposure scenarios needs to consider not only the treated individual animal but must include assessment at population level.

5) There is no guideline detailing data requirements for the exposure assessment. Furthermore the exposure assessment will include different aspects:

   a) Pre-harvest at individual level: The amount/likelihood of resistant bacteria of certain strains present in the gastrointestinal-tract of the treated individual.

   b) Pre-harvest at group level: The number of animals treated and the rate of spread of resistant bacteria between animals.

   c) Post-harvest: Procedures during and after slaughter, including processing, retail and kitchen handling will have impact on the overall exposure to humans. However, these are factors that are fully independent of the use of any antimicrobial in animals and therefore they could only be considered in a general schematic way.

6) The hazard identification and characterisation is substance/class dependent rather than product dependent. It is only the level of exposure of the active component that could differ between products containing the same antimicrobial agent.

7) The company may suggest risk mitigation measures to minimise the risk, e.g. by adding warnings or contraindications to the summary of product characteristics or by restricting the target population for treatment. Therefore, the use of a tiered approach which allows refinements should be made possible.

Therefore, the risk assessment model to be applied will be complicated and also data sources other than data provided by applicant on the specific product (as requested in GL27) will be of importance for the assessment.

3. Discussion (on the problem statement)

Proposals for structures for qualitative risk assessment have been provided both by the World Organisation for Animal Health (OIE) and by Codex Alimentarius. The latter organisation has recently adopted a specific guideline on AMR risk assessment (5) and their risk assessment model will be considered and adapted as appropriate to fit into the concept of approval of VMP.

Codex defines the hazard as a combination of resistance mechanism, bacterium and food commodity and a similar definition would likely be appropriate for the guideline discussed in this concept paper, possibly expanded to cover also some non-foodborne risks. Human exposure to this hazard will depend on a number of factors and among those the intended guideline should focus primarily on factors linked to the veterinary use of the antimicrobial under evaluation. Identification of relevant hazards should be based on GL27 data. In addition, data on drug distribution to and persistence in the gastro intestinal tract (and possibly other body compartments as applicable) need to be evaluated to allow estimation of selection pressure for the hazard. At population level the number of animals to be treated and the production form should be considered.

The endpoint for the assessment on a product level will be the likelihood/amount of resistant bacteria present in (and possibly on) the animal during treatment and at slaughter. To go beyond the pre-harvest stage and estimate the exposure to humans (directly or via food) might be too complicated knowing the number of possible different scenarios. In the Codex guideline presence of resistant bacteria in the animal is accepted as a surrogate marker for the risk for foodborne transmission to humans. It is likely the case also in the guideline intended by this concept paper that presence of resistant bacteria will show to be the endpoint of choice. Nevertheless, a more comprehensive characterisation of the risk to humans covering also post-harvest aspects should be considered as different hazards have more or less severe human health consequences. It is anticipated that this could be covered in general terms by some sort of scheme or template.

The information needed to estimate the exposure is not detailed in GL27 and it is anticipated that further sources of information will be required. However, much of the necessary information is expected to be available elsewhere in the dossier. Information of drug exposure in gastrointestinal tract is provided as a part of the establishment of a microbiological ADI as detailed in VICH GL36 (6). Although the intention of this guideline is to provide data from the human gastrointestinal tract following food intake, much of the information will be applicable also for target animals. E.g. data on faecal binding and data provided to detect changes of resistant bacteria in the colon could be of use. Information on size of target population and details on the production system will be discussed in the clinical part of the dossier. Nevertheless, there will be a need to discuss possible data gaps and determine whether there is a need for further data requirements.

As discussed above, data of relevance for hazard identification/characterisation and post-harvest exposure assessment might be product independent or even totally independent on the antimicrobial agent under assessment. Such data (e.g. data on human food consumption habits and specific data related classes of antimicrobials such as risk profiles) could be provided by making reference to

publically available documents of relevance. In addition it is to be explored to what extent such information could be given as default information in the guideline itself.

4. Recommendation

The CVMP intends drafting a guideline on antimicrobial resistance risk assessment to be applied for all classes of antimicrobial agents. The guideline would apply to all new applications for marketing authorisations including extensions and some variations (where changed doses or new indications are claimed). It might also apply in case of reassessment of existing marketing authorisation for antimicrobial agents, pending outcome of the revision of legislation. The guideline will provide a model for a structured risk assessment based on data requested according to GL27 and other relevant sources.

5. Proposed timetable

Pending comments received drafting will be initiated during spring 2013.

6. Resource requirements for preparation

The drafting will involve a drafting group of people with specific expertise in antimicrobial resistance issues and risk analysis. The group will include members of the EWP-V, SWP-V, AWP, CVMP and, if appropriate, human medicine counterparts. Several drafting group meetings will be needed and possibly also, at a later stage, a focus group meeting with external experts and interested parties involved.

7. Impact assessment (anticipated)

The guideline will provide a basis for transparent and consistent assessment of public health risk related to antimicrobial resistance to be applied both by companies and regulatory bodies. This will be a tool for companies when planning investments in developing new antimicrobials as it will allow for adequate predictability of regulatory decisions. It is not anticipated that the guideline will increase the overall data requirements in terms of number of experiments to be conducted but the applicants may be requested to collect data from different sources and provide a structured assessment of these data to be evaluated by authorities.

8. Interested parties

Veterinary pharmaceutical industry and consultants, regulatory medicines agencies, food safety agencies, scientific committees as applicable covering also human medicine.

9. References to literature, guidelines, etc.

1) VICH GL27, Guidance on the pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL). Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004308.pdf.

2) FDA 152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern. Available from

http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

3) Concept paper on further guidance on interpretation of the data from VICH GL27 (EMEA/CVMP/1034/04- Consultation). Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004313.pdf

4) World Health Organisation, AGISAR 2009. Critically Important Antimicrobials for Human Medicine, 3rd edition

5) Codex Alimentarius Commission GL 77 2012. Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance

6) VICH GL36. Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI