11 April 2011
EMA/CVMP/EWP/760764/2010
Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper on the revision of the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

Agreed by Efficacy Working Party (EWP)	March 2011
Agreed by Scientific Advisory Group on Antimicrobials (SAGAM)	March 2011
Adoption by CVMP	7 April 2011
End of consultation (deadline for comments)	31 July 2011

The proposed guideline will replace the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. Introduction

In 2010 the EWP received a mandate from CVMP for the revision of the existing 'Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances.' The current guideline came into effect in June 2003, and since then, much attention and work have been focusing on the responsible use of antimicrobials in the European Community, especially to reduce the risk of development of antimicrobial resistance. Most recently, the CVMP has finished its work on 'CVMP strategy on antimicrobials 2011-2015' and a revision of the current guideline would follow in line with an updated strategy on antimicrobials.

2. Problem statement

The content of the current guideline originates from 2003. Since then increased knowledge has been gained on several areas relating to the efficacy of antimicrobials, prudent use and development of antimicrobial resistance. Also, during the evaluation of applications for antimicrobial products, many questions and problems have arisen in relation to the adequacy of efficacy demonstration. Therefore, a review of the guideline is appropriate.

3. Discussion (on the problem statement)

The EWP and SAGAM suggest the following points to be included in a revision of the current guideline:

- In line with 'CVMP strategy on antimicrobials 2011-2015', more guidance is needed for products that are, "reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to more narrow spectrum antimicrobials". It should be defined which or on which criteria active substances or product types must be considered as 'second line', and how this should be reflected in the indication(s) and/or other sections of the SPC. In addition, recommendations should be given as to the design of efficacy studies in support of these claims, and to the exclusion of clinical conditions that could be treated with more conventional antimicrobials. Adequate inclusion criteria should be established to reflect the intended use of the product and the target population.
- In case of an outbreak of a disease in a herd it may be relevant from an epidemiological point of view to treat animals which do not (yet) show signs of disease, due to the fact that they are likely infected. However, it is necessary to clarify under which conditions such preventive treatment could potentially be accepted and how this kind of treatment would potentially translate into a claim in the SPC. This should take into account resistance containment, field practices and differences between infection types. Advice on study design should be given to ensure that conclusive data are generated.
- The requirements for use of control groups in laboratory and field studies should be reviewed. In case a positive control is included to explore potential non-inferiority to the medicinal product under study, internal validity of the study should be assessed. Non-inferiority data is often difficult to interpret, especially in situations where substantial self-cure is expected during the course of the study. A negative control may be needed to confirm efficacy and treatment relevance in these situations. Furthermore, a negative control may be needed to confirm the risk for infection in studies for a preventive claim. The guideline should address these situations in more detail.
- In field studies, more precise guidance is needed regarding how to appropriately confirm the etiologic diagnosis and how to establish disease status at the herd level. The diagnostic methods,

proportion of animals to test, and minimum prevalence and severity of the infection have to be specified.

- The option of using PK/PD-data to support the dosing regimen for locally acting products should be explored.
- For systemically acting substances PK/PD data may be used for pre-selection of the dosing regimen. However, the guideline should clarify the requirements that would be put on such data to be regarded as being conclusive. In particular, the adequate PK data should be defined to assess the susceptibility data related to the relevant infection. The relevance of concentrations in plasma, and in tissues and/or secretions, correction for protein binding, etc., should be explored.
- The guideline should clarify in more detail which data would be required to support the treatment duration. It should be indicated whether and which literature data are sufficient and, alternatively, how treatment duration should be optimized through the clinical studies. The effect of treatment duration on potential development of resistance could also be addressed.
- More guidance is needed on post-treatment bacteriological examination and the associated susceptibility testing. Currently it is not clear when it should be performed (in laboratory and/or field studies, in what proportion of the animals and in which animals depending on the clinical outcome), which sampling method is acceptable, which type and number of pathogens from clinical isolates (and commensals, if relevant) and how the resulting re-isolation rate and the possible decrease in susceptibility should be interpreted. Possible use of new diagnostic techniques could be explored.
- Regarding MIC determination, the number of epidemiologically unrelated isolates that can be considered as representative is currently not clear. At least an indicative number of isolates should be mentioned. The number of different geographic areas and livestock production types to consider, and the criteria to select these could be specified.
- The interpretation criteria used to determine level of resistance need to be further explored. In case PK/PD or clinical breakpoints (official or tentative) are referred to these should be justified based on data.
- Duration of the follow-up period to adequately observe cases of relapse should be further specified and defined based on pre-clinical and/or clinical parameters.

4. Recommendation

The Efficacy Working Party (EWP) and Scientific Advisory Group on Antimicrobials (SAGAM) should revise the current guideline. As a consequence of the revision of the guideline, the guideline on the SPC for antimicrobials might also require revision.

A focus group meeting with interested parties might be required.

5. Proposed timetable

Guideline to be drafted by EWP and SAGAM by: 2-3 Q 2012

Expected date for release of draft guideline for public consultation: 3-4 Q 2012

6. Resource requirements for preparation

The revision of the guideline would involve rapporteurs and co-rapporteurs from EWP and SAGAM.

The guideline will be discussed during plenary EWP/SAGAM meetings, and joint drafting group meetings, as needed.

7. Impact assessment (anticipated)

The revision of the guideline will reflect the present strategy of the CVMP in regard to minimising the risk from antimicrobial resistance and to ensure compliance with responsible use principles.

It is expected to provide clearer guidance to applicants, as well as to regulatory authorities, and might impact on the design of clinical trials and provide more precision on the indications. It will also provide a more homogenous assessment of dossiers and fulfil some of the recommendations made by CVMP in their strategy on antimicrobials.

8. Interested parties

Veterinary pharmaceutical industry and consultants, regulatory medicines agencies, scientific committees.

9. References to literature, guidelines, etc.

CVMP strategy on antimicrobials 2011-2015 (EMA/CVMP/287420/2010)

Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01-FINAL)

SPC guideline for antimicrobials