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Committee for Medicinal Products for Veterinary use (CVMP)

Concept paper for the revision of the guideline on the conduct of efficacy studies for intramammary products for use in cattle

Agreed by Efficacy Working party (EWP)	July 2010
Adoption by CVMP for release for consultation	15 September 2010
End of consultation (deadline for comments)	31 December 2010

The proposed guideline will replace guideline on the Conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/344/99-Rev.1)

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

Keywords	*intramammary use, cows, veterinary medicinal product*

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1. Introduction

The current version of the guideline came into force in 1999 and was revised in 2003.
The current guideline concerns mainly antimicrobial products that are administered via the teat canal for treatment and/or prevention of intramammary infections. It therefore addresses antimicrobial treatments for clinical and subclinical mastitis during lactation and the dry period as well as prevention of infections during the dry period.

The guideline is directed towards the design and implementation of field studies on subclinical and clinical mastitis.

Overall, the recommendations made in the guideline are still relevant. However, it is observed that the recommendations are not always followed and, therefore, the text may benefit from clarification on period (dry vs. lactation), type of infection (clinical vs. subclinical) and type of treatment (curative vs. preventive).

Furthermore, new diagnostic methods and treatments are being developed. Although conventional diagnostic methods and treatments still prevail, the guideline should enable the application of new methods.

2. Problem statement

Products used during lactation differ from those used during the dry period, and study designs differ as well. The guideline addresses dry cow treatment and treatment during lactation in separate paragraphs, but in the same sections. The use of separate chapters could be considered, as this allows specification of recommendations per period.

The guideline does not specify causative pathogen species. As lactation and dry period differ with respect to the pathogens involved, studies should address pathogen species and types of infections that are specific for each period, respectively.

Experimental model studies are currently not addressed. The guideline should also include information on such pre-clinical studies that support efficacy.

Trials on mastitis are usually designed as non-inferiority comparisons, between test and authorised reference products. The non-inferiority demonstration might be difficult to achieve for each target pathogen under field conditions due to low incidence. The use of a threshold level for efficacy (e.g. treatment success for each pathogen) could be considered as a means to avoid this dependency.

Studies aiming to demonstrate a preventative claim or aiming to demonstrate a treatment claim for mastitis with known high self cure rate (e.g. E. coli mastitis) are difficult to interpret when only an authorised reference product has been used for comparison. Particularly in these cases, more guidance on the selection of an appropriate control in clinical studies should be given which could include the use of a negative control group.

3. Discussion (on the problem statement)

Type of studies

The current guideline concerns the clinical efficacy of intramammary products when studied under field conditions. On the other hand, justification of claims is frequently based on pharmacodynamic (MIC) and pharmacokinetic data (active substance levels), results from experimental infection studies, and field trials. The guideline should be extended to include guidance on experimental challenge studies, in addition to clinical field trials.

Lactation

For both clinical and subclinical intramammary infections, the success rate should consider potential recurrence of infection/re-infection. Treatment should preferably result in the elimination of pathogens, the reduction of cell counts and the resolution of clinical signs. The prevention of recurrence of infection should be the primary goal.

Pathogens

Efficacy studies should include all major pathogens (*Staphylococcus aureus, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis* and possibly *Escherichia coli*).

Dry period

(Sub)clinical infections can be treated successfully during the dry period, preferably after susceptibility testing. Although there is a risk for infection during the dry period (*E. coli, Str. uberis; A. pyogenes* after teat-damage), it is difficult to demonstrate a preventive effect, as the outcome of a study depends on the level of exposure as well as on the uninfected state of each quarter of the udder. To adequately assess the treatment effect such studies would benefit from the inclusion of an untreated control group.

4. Recommendation

The EWP/CVMP recommends a revision of the existing guideline and to consider the above mentioned issues.

5. Proposed timetable

December 2010	Deadline for comments during public consultation of concept paper
December 2011	Expected date for adoption of the revised guideline by EWP
Q 1 2012	Revised draft guideline for discussion and adoption by CVMP for release for consultation

6. Resource requirements for preparation

Preparation of the revision would involve one rapporteur assisted by two co-rapporteurs.
Preparation of the draft guideline will require discussions at 2 – 3 EWP meetings.

7. Impact assessment (anticipated)

The revision of the guideline is expected to provide clearer guidance to applicants in areas that have caused problems in the past, or which are not addressed in the current guideline.
More detailed information on preclinical issues is expected to result in better knowledge on adequate dosing and application.

8. Interested parties

Pharmaceutical Industry and veterinary consultants.

International Dairy Federation