21 February 2025
EMA/CVMP/EWP/497046/2024
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on the conduct of efficacy studies for intramammary products for use in cattle' (EMA/CVMP/344/1999/Rev.3)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Federation of Veterinarians of Europe (FVE)
2	Société Nationale des Groupements Techniques Vétérinaires - France (SNGTV)
3	Access VetMed

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	FVE supports the draft guideline which aligns the text with the new definitions and terminology of Regulation (EU) 2019/6.	Thank you for your comments.
2	This document gives precise guidelines for the conduct of efficacy trials and that is positive.	Thank you for your comments.
3	Thank you for the opportunity to comment on this concept paper. Overall, the proposals are very welcome by Access VetMed. Consistent use of prophylactic use of antibiotics would not seem to be in line with the most recent advice on prudent use of antimicrobials, perhaps this could be reworded/amended? Reference to the use of products designed to seal the teat canal and not containing any antibiotics, could perhaps be included. Suggest to possibly include reference to contagious mastitis and environmental mastitis pathogens and how these are linked to guideline requirements.	Thank you for your comments. Reference to Article 107(3) of Regulation (EU) 2019/6 is made in section 5.11 of the guideline. Further warnings on prudent use are not considered suitable, as this is a scientific guideline providing advice on how to conduct efficacy studies and not a document giving general advice on how to manage udder disease. No change to the guideline text is considered necessary. Reference to teat sealers has been included in line 77. With regard to the suggestion to include reference to contagious mastitis and environmental mastitis pathogens, the scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, any further in-depth amendments, especially pertaining new requirements, are not foreseen within this revision. However, the comment will be considered in the context of the next revision of the guideline.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
270	2	**Comment**: At what time post the end of treatment must we evaluate the clinical cure?	Accepted. Please refer to lines 340-341 and 349-350. Clinical cure should be evaluated at the time of the first post-treatment sampling, which is 14 to 21 days after the last treatment. The text has been amended in order to provide more clarity.
273	2	**Comment**: At what time must be performed this post-treatment sample for evaluating the cell cure?	Accepted. Regarding treatment of clinical and subclinical mastitis in lactating dairy cows, the second post-treatment sample has to be taken 21 to 28 days after last treatment (please refer to sections 5.9 and 5.10 of the guideline). Regarding treatment of subclinical mastitis at drying off and prophylaxis of new intramammary infections during the dry period, the second post-treatment sample has to be taken 4 to 7 days after the first post-treatment sample, which is scheduled before the first regular milking after calving following the colostrum stage (please refer to section 5.11 of the guideline). Cross reference to those related sections has been added in order to prevent any confusion.
275	2	**Comment**: I think that this mean SCC has little value. Part of cows with SCC under a threshold value would be a better accurate parameter.	Not accepted. The scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, the content of this paragraph was not part of this revision and thus further amendments, especially regarding parameters, are not foreseen within this

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			revision. However, the comment will be considered in the context of the next revision of the guideline.
296	2	**Comment**: How many at most?	Not accepted. The scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the question is appreciated, this paragraph was not part of this revision and thus further amendments, especially regarding changes of requirements, are not foreseen within this revision. However, the question will be considered in the context of the next revision of the guideline.
297	2	**Comment**: during ongoing lactation	Not accepted. The scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, this paragraph was not part of this revision and thus further amendments, especially regarding changes of requirements, are not foreseen within this revision. However, the comment will be considered in the context of the next revision of the guideline.
342	2	**Comment**: OK, that means that clinical cure must be achieved day 14 after the onset of treatment?	Not accepted. Clinical cure must be achieved at the time of the first post-treatment milk sampling (please also refer to line 349). As mentioned in the sentence before, the two milk samples should be taken between day 14 and day 28 after the last treatment, at least 7 days apart. Thus, the first sample can be taken between 14 and 21 days after the last treatment,

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			which is the time for clinical examination. No changes to the guideline text are considered necessary.
346	2	**Comment**: OK, that means that cell cure is evaluated at day 21 or day 28 after the onset of treatment?	Not accepted. SCC shall be measured at the time of the second post-treatment milk sampling. As both milk samples should be taken at any day between day 14 and day 28 after the last treatment and at least 7 days apart, the second sample can be taken between 21 and 28 days after the last treatment. However, "cell cure" is not considered a parameter for treatment success for clinical mastitis; only clinical cure and microbiological cure are considered relevant to determine treatment success (please refer to lines 349-352). No changes to the text are considered necessary.
376	2	**Comment**: All udder quarters with SCC > 200 000 cells/ml or all udder quarters?	Accepted. The respective sentence refers to all quarters of a cow, irrespective of SCC status. Sampling is necessary in order to ensure that inclusion criteria, i.e. only 1 quarter with subclinical mastitis, are fulfilled. The text has been amended in order to prevent any confusions.
390	2	**Comment**: Too inaccurate, that means under 200 000 cells/ml?	Not accepted. The scope of the current revision was to align the guideline to Regulation (EU) 2019/6 and especially Article 4. While the comment is appreciated, this paragraph was not part of this revision and thus further amendments, especially regarding changes of requirements, are not foreseen within this

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			revision. However, the comment will be considered in the context of the next revision of the guideline.
397	2	**Comment**: That means transition to clinical state?	Not accepted. The respective sentence does not make any reference to transition from subclinical to clinical mastitis. It only states that any additional antimicrobial treatment related to the subclinical mastitis would render a case a treatment failure. As this sentence was not part of the current revision of the guideline, no changes are considered necessary.
411-413	3	**Comment**: *For treatment of subclinical mastitis at the time of drying-off, the treatment unit and the statistical unit is the individual quarter. More than 1 quarter can be enrolled and treated per animal.* Is this indicating that separate treatments may be given within the same animal? Due to the potential systemic for systemic absorption, i.e. drug crossing the milk blood barrier, would this be the best study design?	Accepted. The respective sentence was meant to highlight that, if a cow has two or more quarters with subclinical mastitis, those quarters can be included in the trial and each be considered a separate statistical unit and treated with the test VMP. Treatment with different VMPs is not foreseen. However, appropriate statistical methods need to be applied in order to accommodate for clustering of quarters within cow (please refer to lines 469-471). As this paragraph refers to the evaluation of treatment efficacy for subclinical mastitis at drying off, the blood-milk barrier should be intact and, based on available scientific knowledge, any transition of antimicrobials between one quarter and another can be considered negligible and thus no bias regarding efficacy evaluation is expected.

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			Nevertheless, the guideline only mentions that more than 1 quarter from the same animal may be enrolled in the study. It is up to the applicants to decide on which study design is considered the most suitable. In order to provide more clarity, the text has been amended to underline that only treatment with the same veterinary medicinal product is feasible.
463	2	**Comment:** "target", what does it mean: *Staphylococcus aureus*, *Streptococcus agalactiae*, other?	Not accepted. Please refer to the 'Definitions' section (line 569-570). A target udder pathogen is an udder-pathogenic microorganism for which the product is intended to be indicated. No changes to the guideline text are considered necessary.
492	2	**Comment:** clinical mastitis only	Not accepted. The respective sentence as currently written is general and not specific to either clinical or subclinical mastitis. During the current revision, only "bacteriologically" has been substituted by "microbiologically". No further changes to the guideline text are considered necessary.
499	2	**Comment**: In Table 2, I don't understand what you mean when you write: "No of quarters or - at drying off -number of quarters/cows"	Accepted. Thank you for the comment. The treatment unit for subclinical mastitis during lactation and at drying-off is the quarter. The text has been amended accordingly.
511	3	**Proposed change**: Suggest including a suitable non-inferiority margin?	Not accepted.

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			While this paragraph has been partly revised, changes do not pertain requirements for equivalence between candidate and reference products. Thus, albeit the proposal is appreciated, it is not within the scope of this revision to add or lessen any requirements, such as a currently not specified non-inferiority margin. However, the comment will be considered in the context of the next revision of the guideline.
544	2	**Comment:** More precision is needed: SCC > 200 000 cells/ml.	Partly accepted. While the comment is appreciated, "elevated SCC" without a clear numerical definition was already part of the previous version of this guideline. As the scope of the current revision was to align the guideline to Regulation (EU) 2019/6, further amendments were not foreseen within this revision. However, the text has been amended for clarity purposes to include reference to 'elevated milk somatic cell count beyond physiologically normal concentrations'.