18 February 2016
EMA/CVMP/EWP/335976/2014
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on Guideline on the conduct of efficacy studies for intramammary products for use in cattle (EMA/CVMP/EWP/141272/2011)

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

Stakeholder no.	Name of organisation or individual
1	IFAH-Europe
2	EGGVP – European Group for Generic Veterinary Products

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe welcomes the opportunity to comment on this guideline. We appreciate the continued separation of intramammaries from the guideline on demonstration of efficacy for veterinary medicinal substances containing antimicrobials and the updating of this guideline as appropriate. The addition of a glossary providing definitions of the terms used (e.g. first regular milking) would greatly aid the clarity of the guideline.	The term “first regular milking” has been further specified in the guideline text.
2	EGGVP welcomes the publication of this draft guideline; in particular the fact that there is a specific section for data requirements for generic products is a positive aspect of the guideline.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
69-75	1	**Comment:** This paragraph references the current guideline for the Demonstration of Efficacy for Veterinary Medicinal Products containing Antimicrobial Substances (EMEA/CVMP/627/2001) a revised version is currently in development and this reference should be updated if and when the revision is approved. Should guideline EMEA/CVMP/644/2004 be referenced here as well?	- Accepted to update the reference to the revised antimicrobial guideline once approved. - It is felt that the guidance CVMP/VICH/644/01-Final (2004) is meant here. The proposal to include the reference regarding 'guidance an pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance' (CVMP/VICH/644/01-Final, 2004) is supported since systemic absorption of an antimicrobial following intramammary administration cannot be excluded (the extent of absorption is a variable factor and will probably depend on the properties of the product and the kind of changes in the tissue of the mammary gland) and in addition, pathogens with relevance for human beings are concerned (e.g. *E. coli, Staph. aureus, entercocci*).
84-92	1	**Comment:** Adverse events are not considered as PD related and would be better placed in a Target Animal Safety section.	Accepted.
98	1	**Proposed change: "**the concentration **time** profile**."**	Accepted.
106-112	1	**Comment:** The aspects listed (pathogens, doses, dosing intervals, treatment durations) should not only be considered in the dose determination section. Other	Partly accepted. A section concerning dose selection principles has been

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		ways to address them should be acceptable: e.g. PK-PD, published literature on the disease, dose-confirmation. **Proposed change:** we suggest the section is restructured as follows: 5. Clinical studies 5.1 Dose selection principles Then add lines 108-112 to this section as these lines apply to all studies 5.2 Dose determination studies 5.3 Dose confirmation studies 5.4 Field studies	included and the structure of the clinical section has been revised. Dose determination studies are indispensable and cannot be replaced by PK-PD analyses or published literature. Published literature is only accepted as supportive information.
115-116	1	**Comment:** If the dose is not available yet, the final formulation cannot be defined. **Proposed change: "**Where possible, the **near to** final formulation of the test product should be used."	Accepted. However, this is adequately expressed by the words "where possible". Therefore, no change of the wording is necessary.
117-8	1	**Comment:** It makes sense that a negative control group is included in an experimental model. However, if the study has to take place in naturally infected animals (see lines 135-6), such a control may not always be acceptable for animal welfare reasons. It is noted that the lack of a negative control is accepted in certain cases of dose confirmation studies (144-6). It should also be noted that this is a guideline and as such the "mandatory" is too strong. **Proposed change:** "**Unless justified**, the inclusion of	Not accepted. Especially at the level of dose determination a negative control is needed and justified to get meaningful results. Dose determination studies will usually be performed with a low number of animals per study group preferably under controlled clinical conditions. As a follow up of dose determination the lack of a negative control group in dose confirmation studies may be accepted under certain study conditions. The wording of the sentence in question (in the section "Dose

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		a negative control group is ~~mandatory~~**recommended**".	determination studies") has been modified. It reads now: Dose determination studies should always include a negative control,…".
128	1	**Proposed change:** …should be considered, **e. g. inclusion of more than one quarter per cow if justified. Also experimental studies in other animal species can reduce the number of studies in the target species if justified.**	Not accepted. Particularly in lactating cows with clinical mastitis in more than 1 quarter an interference between affected udder quarters cannot be excluded. Thus, quarters could not be regarded as independent. In addition for the purpose of dose determination no reliable data base is available which would allow an extrapolation from experimental studies in other animal species to cows. Therefore, the proposed sentences have not been introduced in the guideline. The information with regard to 3Rs has been deleted here and is given in section 3.
148-150	1	**Comment:** A waiver for dose confirmation studies is considered. It would be helpful to give examples. **Proposed change:** "… naturally occurring infections (**e.g. line extensions**,…)	Accepted. The respective paragraph was drafted to reflect in a general way the respective wording in the antimicrobial guideline, section 6.3. In order to provide more information the relevant conditions for a waiver for dose confirmation studies have been further explained in this guideline.
167-168	1	**Comment:** Limiting positive controls to those with the same proposed indications as existing products also limits innovation and extension to include other pathogens not currently "covered" by reference products. Previous wording was softer: "where possible	Not accepted to include the words "where possible". In principle, the positive control should cover the indications etc. as claimed for the test product to allow for a comprehensible assessment of efficacy. Innovations and extensions are not considered to be limited by the guideline

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		it is “advisable” to use a reference product” **Proposed Change:** The positive control **where possible** should be an intramammary product with the same indications as the test product…	text because at the end of the respective paragraph it says “In the absence of a suitable positive control the applicant should seek scientific advice from the authorities”.
172	1	**Comment:** products where posology differs between Member States should be avoided (as positive control). This doesn’t leave a great choice of control products… **Proposed change:** should be avoided**, if possible**.	Not accepted to include “if possible”. It is indicated at the end of the 3rd paragraph that “in the absence of a suitable product as positive control the applicant should seek scientific advice from the authorities”.
176	1	**Comment:** Will all MSs permit this on welfare grounds? Farmers may be reluctant to leave an infected quarter untreated. Use of a negative control group in preventive field studies at drying off may also increase the risk of a chronic infection (followed by replacement of the cow) even in situations where high self-cure can be expected. **Proposed change:** Comparison with a negative control is also ~~considered necessary~~ **recommended** for infections…	Not accepted to soften the requirements. At present there are no reports that a negative control group with uninfected cows (having a low individual somatic cell count) at drying off will endanger animal welfare (e.g. according to experience in the Netherlands). However, the wording has been modified to be more in line with the same issue in the antimicrobial guideline (section 6.4.2). It now reads as follows: A negative control is considered necessary for …(instead of mandatory).
177	1	**Comment:** There are subclinical infections which have a low spontaneous cure rate (ca. 20% for *S.aureus* subclinical mastitis during lactation). **Proposed change:** (e.g. **some** subclinical infection at drying-off~~, E. coli infections~~)	Partly accepted. It is agreed to add “some” so that it reads “some subclinical infections”. However, there is no reason to restrict this to the time at drying off. Regarding E. coli it should be noted that such infections are known for high self cure rates. Therefore, this is a valid example. For further clarification the wording has been modified as follows: E. coli infections in the status of

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			lactation.
182	1	**Comment:** We consider that in some cases a group of mastitis causing bacteria within the same genus, e.g. Coagulase Negative *Staphylococcus* (CNS) including all different CNS species, could be considered as a target pathogen group. **Proposed change:** A claim for efficacy should be demonstrated for each target pathogen **or a target pathogen group** separately.	Partly accepted. With view to CNS which are known to be normally treated as a uniform group it is agreed to include a target pathogen group. However, the sentence should read as follows: "A claim for efficacy should be demonstrated for each target pathogen separately or for a target pathogen group if scientifically justified (e.g. CNS)."
184-186	1	**Comment:** It is stated that, in general, the clinical study should be sufficiently powered to demonstrate a statistically significant effect for each claimed bacteria species separately. This could easily require total animal numbers approaching 1000 or more, which would be impossible to achieve. We suggest considering an overall significant effect including all pathogens, and then derive label pathogens by those that appear in numerically greater and clinically relevant cure numbers. As an example, US-CVM requires a minimum of 30 cases that meet those criteria. **Proposed change:** The clinical study should be sufficiently powered **to demonstrate an overall statistically significant effect. The applicant should subsequently justify the choice of the claimed pathogens.**	Not accepted. Mastitis is a common disease und there should be no problems to recruit an adequate number of animals. The wording in the guideline is considered acceptable as it also addresses field situations with less common pathogens. In sum the current text proposal allows for some flexibility.

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191	1	**Comment:** The US National Mastitis Council documents are recommended which further supports the international aspects of guideline drafting. As there are multiple documents available, it is not clear which one(s) are appropriate. http://www.nmconline.org/documents.html	Not accepted. It is not considered necessary to include further/more detailed information. The guideline mentions the NMC in connection with milk sampling and microbiological investigations. It should be possible to find relevant documentation on the website of the NMC. As indicated other adequate references can also be used.
193-195	1	**Comment:** It is justified to sample all 4 quarters at inclusion in the case of subclinical mastitis but not in the case of clinical mastitis. We consider that in case of clinical mastitis it should be enough to take the pre-treatment milk sample for bacteriological examination from the affected udder quarter only. The selection of the affected udder quarter in clinical mastitis can be made based on clinical signs of the udder or changes in milk. **Proposed change:** For recruitment **of cows with subclinical mastitis**, bacteriological examinations of milk samples should be performed from all udder quarters of any cow in order to meet the inclusion criteria. **In case of clinical mastitis, pre-treatment bacteriological examination can be performed from the affected udder quarter only, based on clinical signs.**	Accepted.
206	1	**Comment:** Exclusion criteria only permit one infected quarter though; should this read per quarter?	The information that the bacteriological status (primary parameter) should be evaluated for each included udder

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			quarter is given in the general part which is valid for conditions during lactation and at drying off. The wording is clear and does not need further explanation.
216-217	1	**Comment:** The requested information on herd and especially cow history might not always be available. **Proposed change:** **To the extent possible**, the history of the herd and cows should be recorded…	Accepted.
220	1	**Comment:** Inclusion of the name and address could be challenging from a legal perspective (privacy) in some member states. We would suggest the name and address are included in the trial master file to protect privacy and/or the following amendment. **Proposed change:** "Name and address **or farm code and district / region** of herd owner."	Accepted.
225	1	**Comment:** We consider that the requirement of bulk milk SCC in the herd over several months is not always possible to fulfil. **Proposed change:** • Bulk milk SCC in the herd over preceding months**, if available**.	Text proposal not accepted. Usually such data should be available. In addition, in the introduction it is said "to the extent possible".
233-234	1	**Comment:** We consider that the requirement of SCC of cow's milk over several months, or the history of previous mastitis treatments is not always possible to fulfil. **Proposed change:**	Text proposal not accepted. Usually such data should be available. In addition, in the introduction of this chapter it is said "to the extent possible".

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		• Cow milk SCC during preceding months**, if available**; • History of previous mastitis treatments**, if available**;	
245	1	**Comment:** Suggest amending 'vaccinated' to 'treated' as not all products inducing an immune mediated response are vaccines. **Proposed change:** Cows ~~vaccinated~~ **treated** with products inducing an immune-mediated response against mastitis pathogens.	Accepted.
248	1	**Comment:** Severe clinical signs may be an inclusion criterion. **Proposed change:** "In clinical mastitis: cows with severe systemic clinical signs **(as appropriate)**."	The proposal to add "(as appropriate)" is unclear and has therefore not been introduced. However, the wording has been modified by adding "requiring systemic treatment".
249	1	**Proposed change:** "In clinical mastitis: cows with ~~mastitis~~ **clinical signs** in two or more udder quarters".	The sentence has been revised and reads now: In clinical mastitis: cows with clinical signs of mastitis in two or more udder quarters.
249 + 256-257, 264-265, 384-387	1	**Comment:** Why have cows with mastitis in two or more udder quarters to be excluded from the trial, if no systemic clinical signs are present? As cows frequently develop mastitis in more than one quarter, excluding those animals will unnecessarily increase animal numbers in a trial although these animals also present a part of the population which later will be	Proposed text modification not accepted. In case of clinical mastitis the restriction to one quarter is generally accepted in order to avoid any influence from treatment of other quarters. This is considered important especially for the evaluation of efficacy. Once efficacy has been proven for cows with 1 mastitic quarter it will, of course, be inferred to cows with mastitis in more than 1 quarter.

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		treated with the commercial product. **Proposed changes:** Line 249: In clinical mastitis: cows with mastitis in two or more udder quarters**, if systemic clinical signs are present.** Line 256: Delete the words "limited to 1 quarter" Lines 264-265: In any included cow only the ~~single~~ affected quarter**(s)** will be treated. A cow developing clinical mastitis in additional quarters during the experimental period **and showing systemic clinical signs** should… Line 386: **"…**treatment group, **if systemic clinical signs are present."**	
260-262	1	**Comment:** We consider that in case of clinical mastitis it should be enough to take the pre-treatment milk sample for bacteriological examination from the affected udder quarter only. The selection of the affected udder quarter in clinical mastitis can be made based on clinical signs of the udder or changes in milk. **Proposed change:** Before treatment one milk sample **from the affected udder quarter** should be taken for bacteriological analysis and determination of quarter milk SCC and the cow should be clinically examined (general condition, appearance of milk, udder consistency).	Accepted. With view to the comment regarding line 193-195 the proposal is logical.
273-274	1	**Comment:** It is stated that quarter milk SCC should	Accepted, it is correct that no second sample for quarter milk

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		be determined from the second post-treatment sample. In lines 271-272, however, it is indicated that clinical failures at the first post-treatment sampling point should be excluded from further sampling. The latter implies that, from such cases, no second sample will be available to determine quarter milk SCC. Please confirm or amend.	SCC will be available in such a case.
279	1	**Comment**: The term a bacteriological cure requires further explanation as to its exact definition for the purposes of this guideline; cure implies sterility but microbiologically it is below the level of detection (dependent on the dilution scheme and media used). **Proposed change:** Please clarify either in the text or the glossary proposed the general comments section.	The wording in brackets explains what bacteriological cure is for the purpose of this guideline (i.e. absence of the udder pathogen species which was present at the time of inclusion). No further explanation is considered necessary.
281-282	1	**Comment:** The sentence as written is not understandable: **Proposed change:** ~~Quarters~~ **Cows** with new infections in the originally infected, treated quarter (i.e. detection of an udder pathogen which is different from that isolated at inclusion in one or both post-treatment milk samples**)** can be classified as a bacteriological cure for the original pathogen."	Accepted.
285	1	**Comment:** "A high frequency of these occurrences is not acceptable" It is not clear what the consequences would be (invalidation of the study and need to set up	Accepted.

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		a new one?). New infections are inevitable and unpredictable. A new infection associated with mastitis clinical signs will already be classified as a failure (see 277-280). In the case there is no mastitis clinical signs, but just a positive bacteriology and an elevated SCC level, a thorough analysis (by farm) should be conducted. **Proposed change:** A high frequency of these occurrences **requires a thorough analysis** ~~is not acceptable~~.	
289-290	1	**Comment:** It is stated that if the original pathogen is detected in one or both of the post-treatment samples the case is regarded a clinical failure. However, lines 279-280 imply that, if a different pathogen than the one at the time of inclusion is detected, one can still consider the case as a treatment success. What if the post-treatment sample(s) show(s) the presence of the same pathogen that was detected originally, but it can be shown with molecular techniques that it is a different strain of the pathogen than that which caused the initial infection? Could this be considered a treatment success, or if not, why not. Please clarify.	If a study uses molecular diagnostic techniques and it can be proven that the pathogen belongs to a different strain compared to the original pathogen, ruling out mutations or resistance selection, it can be concluded that a new infection has occurred. Therefore, this could be regarded as a treatment success. However, diagnostic methods will not be specified in the guideline. It is up to applicants to address the diagnostic methods in the study protocol.
291-292	1	**Comment:** There appears to be a typo/missing part in this sentence. **Proposed change:** If additional antimicrobial	Accepted.

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		treatment associated with the mastitis **case enrolled** is necessary during the experimental period.	
300-301	1	**Comment:** We assume that different pathogens can be permitted in those quarters. **Proposed change:** More than one quarter may qualify for inclusion~~.~~ , **pathogens may differ between quarters.**	Not accepted. Only cows with one subclinically infected quarter qualify for inclusion. The reason is that a difference in the response to treatment between cows with one affected quarter and cows with more than one affected quarter have to be taken into consideration for the efficacy evaluation. Moreover, interference between quarters cannot be excluded. Consequently, the option that pathogens may differ between quarters cannot be taken into account.
303	1	**Comment:** We consider that sampling in subclinical and clinical mastitis should be differentiated more clearly. **Proposed change:** Before treatment two quarter milk samples **from all udder quarters** should be taken one to three days apart for bacteriological analysis; if a pathogen can only be isolated from one out of these two samples, diagnosis should be confirmed with a third sample.	Accepted.
303-305 345-346	1	**Comment:** It is stated that, if only one of a duplicate sample is positive, a third sample should be taken for confirmation. Given the incubation time required for bacterial isolation and identification, results will not necessarily be available in a timely manner i.e. before treatment is initiated, and as such, a third sampling	Not accepted. The time period between the first and the second sampling is one to three days. So the first and second samples are taken consecutively. It is not a duplicate sample. Should a third sample be necessary the same applies for the time period between the second and the third sample. The strategy is in

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		will not be feasible. **Proposed change:** Please delete 'if a pathogen can only be isolated from one out of these two samples, diagnosis should be confirmed with a third sample'.	principle not different from the currently valid guideline.
318	1	**Comment:** Possible cases when the original pathogen is not detected in the post treatment samples but the somatic cell count is high are not described. **Proposed change:** Please change sentence to: "…milk samples. ~~Supported by a~~ **A** decrease in the somatic cell count **is considered supportive**."	In principle accepted. The sentence has been modified as follows: "A marked decrease in the somatic cell count is considered supportive".
341	1	**Comment:** Typo a space is needed between "approximately" and "35". **Proposed change:** "… approximately 35 days …"	Accepted.
378	1	**Comment:** This sentence would merit the following specification: **Proposed change:** If additional antimicrobial treatment **related to mastitis** is necessary during the experimental period.	Accepted.
393-397	1	**Comment:** It would not necessarily be elegant to capture all this information in the clinical study reports. It could also be appropriate to present such data through separate reports or statistical data listings. **Proposed change:** '… a record from each individual case should be presented in the **dossier**' … 'In vitro	Accepted.

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		susceptibility results should be enclosed in the **dossier**'.	
398-399 and Table 1	1	**Comment:** If the comment to lines 249 et al is not accepted In the case of clinical mastitis, only one quarter per animal can be enrolled. The number of quarters cured would therefore be equal to the number of cows cured. Only for subclinical mastitis it could be relevant to present the data separately for number of quarters cured vs number of cows cured. This might merit clarification in the text and tables.	Accepted to provide clarification. Text and tables have been modified. . However, it should be noted that for the purpose of the guideline the requirements concerning efficacy trials for subclinical mastitis during lactation have been changed following careful consideration of factors (e.g. difference in response to treatment between cows with 1 affected quarter and cows with more than one affected quarter, interference between udder quarters) which could affect efficacy assessment. Please, refer to part 5.4.10 of the guideline.
421	2	**Comment**: Clarification on the justification requested would be helpful. What type of data is considered suitable to justify that a target pathogen is the most difficult one to treat in vivo ?	A clarification has been added. It reads now "…the most difficult to treat *in vivo* based on pharmacokinetic properties, pathophysiological characteristics and susceptibility of the target pathogen(s), as appropriate".
422	1	**Comment:** Please add 'safety' as well. **Proposed change:** parameters for evaluation of efficacy **and safety** in field trials apply.	In principle accepted. Instead of safety the term tolerance was introduced.
425-428	1	**Comment:** Does "specific efficacy (and safety) studies may be waived" mean that in this case no efficacy and safety studies will be required at all? **Proposed change:** Please specify minimum requirements for efficacy and safety studies, if any, or that in this case no such	Accepted. With regard to waiving efficacy/(tolerance) studies the minimum requirements have been specified. With regard to efficacy an annex with further details has been provided.

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		studies may be required.	
425-428	2	**Comment:** Getting information on the exact formulation of the reference product is nearly impossible. If only this option for a generic based on identical formulation is included, it will be very difficult to develop a generic product based on the conditions to fulfil. The Guideline on the conduct of bioequivalence studies for veterinary medicinal products includes another option for a waiver mentioned being: *"For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance."* EGGVP wonders if this waiver was also considered for inclusion this draft guideline? If so, what were the reasons for exclusion?	Not accepted. The option cited from the bioequivalence guideline is not considered applicable for intramammary products. Please, note that with regard to waiving efficacy/(tolerance) studies the minimum requirements have been specified and with regard to efficacy an annex with further details has been provided.
432-434	1	**Comment:** We consider that the definition of clinical	Accepted.

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		mastitis includes clinical signs in one or more quarters or changes in the appearance of milk with or without general signs. In other words in some cases it is possible that changes in the appearance of milk can be seen without clinical signs of the affected quarter, and that should be classified as clinical mastitis too. **Proposed change:** Clinical mastitis is defined as mastitis with clinical signs in one or more quarters (swelling, heat, pain, redness) and***/ or*** changes in the appearance of milk (cloths or flakes, watery appearance, discoloration), with or without general signs (fever, loss of appetite).	