EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2024
EMA/CVMP/QWP/426122/2023
Committee for Veterinary Medicinal Product

Overview of comments received on 'Guideline on Quality Aspects of Pharmaceutical Veterinary Medicines for administration via drinking water - Annex on compatibility studies between veterinary medicinal products and biocidal products' (EMA/CVMP/QWP/592906/2022)

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

Stakeholder no.	Name of organisation or individual
1	Access VetMed

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	Once again, Access VetMed appreciates the opportunity to comment in this Guideline proposed by EMA. Please refer to the next page for specific comments on the text proposed.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 54-55	1	Comment: It would be hard storing these vessels (up to 6 in parallel according to the example provided in the draft guideline) in climatic chambers to ensure constant temperature of 25°C. In a lab usually room temperature of 20 – 25°C is ensured. It would be good to have also the term "at room temperature" or a range of 20 – 25°C as possibility (maybe with the addition that the temperature has to be monitored and documented) Proposed change (if any): "Samples of the medicated drinking water should be stored at **a monitored and controlled temperature of 20-**25°C".	No change - with the stability studies, the principles of the parent guideline should be followed. This parent guideline states "Samples of the medicated drinking water should be stored at 25°C". In-use stability studies with biocides should be performed in the same conditions.
Lines 57-58	1	Comment: Due to the dilution of the veterinary medicinal product in drinking water (typically 1:1000, or sometimes lower), it may be challenging to study degradation products down to the VICH quantification threshold of 0.3%. Therefore, CVMP is kindly asked to add some provision to deal with cases like these. Proposed change (if any): Nonspecific. See above comments.	No change - Principles of the parent guideline should be followed. In this parent GL, it is stated in section 9 and appendix 2 "Physical and chemical properties (***such*** as appearance, assay and levels of degradation products) of the medicated drinking water should be studied"; then, if the analytical method is capable to determinate degradation without biocides, it should be also capable to demonstrate degradation with biocide.
Line 63	1	Comment: Access VetMed understand that if successful data	To modify the "sampling time points (h)"

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		is presented for the sampling time points at T=0 and 24 hours, the T=12-hour time point may become irrelevant, so the possibility of 'bracketing' should be contemplated. Proposed change (if any): "T_0, T_{12} **(if considered necessary)**, T_{24}".	column as such : T_0, T_x, T_{24} (*other time points could be used depending on the proposed shelf-life ; max. 24 hours*)
Lines 73-76	1	Comment: AVM supports using the concentration of 1 ppm active chlorine (as per EU standards) as valid, as requiring biocides being dosed as labelled could make the results difficult to compare in case pharmaceutical companies use different brands of biocides for the tests. Having said the above, AVM consider completely unnecessary having to develop and validate additional methods to quantify chlorine in water. AVM consider that after taking the label claim of the specific biocide to be used for the study, the Applicant should be in a position to prepare a resulting water solution with a final theoretical concentration of chlorine at 1 ppm without the need of any further tests. In case CVMP may still not consider this adequate, it should definitely be listed that the amount of chlorine is to be quantified at T_0 before the medicinal product is added. Reason being the fact Applicants should then develop and validate method for each finished product, as the active substances (or possibly excipients such as antioxidants) present in the finished product might have also redox	To change "In order to calculate the amount of chlorine to add (chlorine dioxide ClO2, sodium hypochlorite NaClO) to obtain 1 ppm of active chlorine, a validated analytical method should be used, e.g., by titration with sodium thiosulfate. **Active** chlorine should be quantified (***before*** the addition of the veterinary medicinal product to be assessed) to verify that the correct quantity of active chlorine is obtained in the solution". Because the quantity of real active chlorine content depends of the temperature and hardness of water used, the 1ppm of active chlorine before adding the veterinary medicinal product should be strictly controlled. References to be added: *Black & Veatch Corporation. White's Handbook of Chlorination and Alternative Disinfectants –*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		properties, so a basic (unspecific) titration method like the proposed one may not be sufficient. Proposed change (if any): **Most preferred:** "In order to calculate the amount of chlorine to add (chlorine dioxide ClO2, sodium hypochlorite NaClO) to obtain 1 ppm of active chlorine, **the Applicant should perform the relevant dilution based on the label claim of the biocide to be used in the study.** ~~a validated analytical method should be used, e.g., by titration with sodium thiosulfate. Chlorine should be quantified at least at T0 to verify that the correct quantity of active chlorine is obtained in the solution.~~" **Less preferred:** "In order to calculate the amount of chlorine to add (chlorine dioxide ClO2, sodium hypochlorite NaClO) to obtain 1 ppm of active chlorine, a validated analytical method should be used, e.g., by titration with sodium thiosulfate. Chlorine should be quantified at least at T0 **(before the addition of the veterinary medical product to be assessed)** to verify that the correct quantity of active chlorine is obtained in the solution".	*5th ed (p. 74). Wiley. Kindle Edition.* *Pool water treatment advisory group: https://www.pwtag.org/importance-of-free-chlorine-content-tn60/*