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Committee for Veterinary Medicinal Products (CVMP)

Guideline on Quality Aspects of Pharmaceutical Veterinary Medicines for administration via drinking water - Draft Annex on compatibility studies between veterinary medicinal products and biocidal products

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

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APPENDIX 2:

Compatibility studies between veterinary medicinal products and biocidal products

At farm level, biocidal products may be used to reduce microbial contamination of drinking water for animals or for the disinfection of equipment, surfaces or pipework associated with the production, transport, storage or consumption of feed and drinking water for animals. Studies have demonstrated that biocidal active substances may induce degradation of some veterinary medicinal products (VMPs) administered via drinking water, which may result in treatment failures (i.e., lack of efficacy) and/or increase the risk of antimicrobial resistance.

Therefore, potential interactions between commonly used biocidal active substances and VMPs administered via drinking water should be studied and appropriate information regarding incompatibilities should be provided in the product information, where relevant. If, based on literature, it is established that the VMP is incompatible with biocidal active substance(s), the relevant information should be included in the product information without the need to conduct a specific compatibility study.

The stability of VMPs to be administered via drinking water should be tested in the presence of biocidal active substances for the duration of the in-use shelf-life, usually 24 hours. Several biocidal products to disinfect drinking water for animals are commercially available(1). Testing of at least two different biocidal active substances belonging to product-type 5 (PT5)(2) should be performed. Product-type 5 are biocidal products used for the disinfection of drinking water for both humans and animals. Biocidal products containing chlorine and hydrogen peroxide are the most common in Europe for such use. Therefore, their use is recommended for comparison purposes. Selection of other biocidal active substances may be justified based on pattern of use in the Concerned Member States. This can be supported by scientific publications or other relevant sources of information, which should be provided in the dossier.

In the proposal below for the preparation of chlorine and hydrogen peroxide treated water, the concentration specified for each biocidal active substance is in line with the EU standard for treatment of water intended for human consumption and only this concentration will be usually required. Only biocidal products authorised under regulation 528/2012 should be used in the tests. However, it should be noted that higher concentrations of biocidal active substances in drinking water may be authorised for use depending on factors such as target species, water hardness, microbial contamination etc. Therefore, in addition to standard concentrations detailed in the section on treated water below, higher concentrations can be tested, if appropriate e.g., if relevant for the target species. This can be supported by scientific publications or other relevant sources of information, which should be provided in the dossier.

The stability of medicated drinking water at the lowest nominal concentration of the VMP that is specified in the product information should be investigated. Two different qualities of drinking water (soft and hard water) should be used to prepare the medicated drinking water. Appendix 1 includes information on the two different water qualities that should be used for such studies. Samples of the medicated drinking water should be stored at 25°C. The storage vessel used should simulate the container(s)/contact parts of the water supply system likely to be present during administration of the product e.g., plastic bucket, metal pipework. Physical and chemical properties (such as appearance, assay and levels of degradation products) of the medicated drinking water should be studied.

The results of these studies should be provided in part 2.F.2. of the dossier. Preparation of the water and calculation of the biocidal active substance concentrations should be clearly detailed. The principles

of the parent guideline should be followed. A single study can be designed to address both the in-use stability study of the VMP in drinking water and its compatibility with biocides. One example of such a study design is given below:

Type of water	Solutions with the VMP to be tested	Sampling time points (h)
Soft water	Water without biocidal active substances	T_0, T_{12}, T_{24}
	Water with biocidal active substance 1	
	Water with biocidal active substance 2	
Hard water	Water without biocidal active substances	
	Water with biocidal active substance 1	
	Water with biocidal active substance 2	

Preparation of treated water

- Preparation of water with chlorine

A concentration of 1 ppm of active chlorine (active or available chlorine, sum of HOCl + OCl^-), in line with the EU standard for chlorine treatment of water for human consumption [3, 4], is generally considered suitable. Active chlorine concentration differs from free chlorine concentration depending on the conditions such as temperature, pH and water hardness e.g. at 25°C 1 ppm active chlorine can be equivalent to 1.3 ppm of free chlorine in soft water (pH 6) and 22 ppm of free chlorine in hard water (pH 8).

In order to calculate the amount of chlorine to add (chlorine dioxide ClO_2, 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 T_0 to verify that the correct quantity of active chlorine is obtained in the solution.

Different qualities of chlorine with or without stabiliser are available on the market. Information regarding the name of the biocidal active substance (e.g., active chlorine generated from chlorine dioxide ClO_2, sodium hypochlorite NaClO) and its concentration should be given. If applicable, the name and concentration of any relevant non-active substance in the biocidal product (e.g., stabilisers) should also be included.

- Preparation of water with hydrogen peroxide

A concentration of 35 ppm of hydrogen peroxide (expressed as mass fraction of 100% hydrogen peroxide), in line with the EU standard for hydrogen peroxide treatment of water for human consumption [5], is generally considered suitable. As different qualities of hydrogen peroxide are available on the market, information regarding the name of the biocidal active substance and its concentration should be given. If applicable, the name and concentration of any relevant non-active substance in the biocidal product (e.g., stabilisers) should also be included.

Product information

The brand name of the biocidal product(s) used in the tests should also be given in the dossier but it will not be given in the product information of the VMP. The following sentence(s) should be included in Section 3.9 of the Summary of Product Characteristics and Section 9 of the Package Leaflet, as appropriate:

- This veterinary medicinal product must not be administered using drinking water containing [name of biocidal active substance 1, e.g., chlorine] <or [name of biocidal active substance 2, e.g., hydrogen peroxide]> as the active substance [name of active substance] degrades in the presence of <this biocidal active substance > <these biocidal active substances >.
- This veterinary medicinal product may be administered using drinking water containing [name of biocidal active substance 1, e.g., active chlorine] at a maximum concentration of [XX] ppm <and [name of biocidal active substance 2, e.g., hydrogen peroxide] at a maximum concentration of [YY] ppm.

REFERENCES

(1) https://echa.europa.eu/regulations/biocidal-products-regulation/authorisation-of-biocidal-products

(2) Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products

(3) EN 937:2016: Chemicals used for treatment of water intended for human consumption - Chlorine

(4) EN 12671:2016 Chemicals used for treatment of water intended for human consumption – Chlorine dioxide generated in situ

(5) EN 902:2016: Chemicals used for treatment of water intended for human consumption – Hydrogen peroxide