EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2022
EMA/CVMP/QWP/697426/2021
Committee for Veterinary Medicinal Products

Concept paper on the need for amendment of Guideline on Quality Aspects of Pharmaceutical Veterinary Medicines for administration via drinking water - Annex on the concomitant use of Veterinary Medicinal Products and biocides.

Agreed by Quality Working Party	November 2021
Adopted by CVMP for release for consultation	19 January 2022
Start of public consultation	28 January 2022[1]
End of consultation (deadline for comments)	30 April 2022

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

Keywords	Veterinary medicinal product, Biocides, Drinking water

1. Introduction

The Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products (repealing Directive 2001/82/EC) entered into force on 28 January 2019 and is applicable from 28 January 2022 onwards. One of the scientific and technical recommendations prepared by the EMA to feed into delegated and implementing acts as part of the implementation of the Veterinary Medicines Regulation, concerns oral veterinary medicinal products administered via routes other than medicated feed. The expert group appointed under the EU mandate (Ref. Ares (2019)4154270 - 01/07/2019)(1) for the new veterinary regulation (EU 2019/06) to establish rules for

[1] Date of publication on the EMA public website.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

the administration of oral products, included in its report a number of recommendations, one of which relates to the use of biocides in the water used to administer oral veterinary medicinal products.

This concept paper addresses the need to complement the guideline on Quality Aspects of Pharmaceutical Veterinary Medicines for administration via drinking water (EMEA/CVMP/540/03 Rev.1)[(2)] with information relating to the use of biocides in the water used to administer these oral Veterinary Medicinal Products. The scope of any additional guidance developed will be the same as that of the parent guideline.

2. Problem statement

The quality of water is an important aspect for Veterinary Medicinal Products administered via drinking water as highlighted in the parent guideline on Quality aspects of pharmaceutical veterinary medicines for administration via drinking water (EMEA/CVMP/540/03 rev.1). This guideline covers characteristics of water such as pH and hardness, which can affect the solubility and/or stability of the active substance, but it does not include any information regarding the presence of biocides commonly used in the treatment of the water.

The advice on implementing measures under Article 106 (6) of Regulation (EU) 2019/6 on veterinary medicinal products – *scientific problem analysis and recommendations to ensure a safe and efficient administration of oral veterinary medicinal products via routes other than medicated feed*, published in August 2020(EMA/CVMP/508559/2019)[(3)], includes the following statement in relation to biocides:

"At farm level, biocides may be used to reduce microbial contamination of drinking water. However, concomitant administration of biocides and veterinary medicinal products in drinking water may affect the veterinary medicinal product. Studies have demonstrated that biocides may decrease the stability of certain antibiotics administered via drinking water, which may result in treatment failures and/or increase the risk of development of resistance. Biocides may also adversely affect the viability of bacteria/viruses included in live vaccines leading to a reduced efficacy."

The advice includes the following recommendation:

"Potential interactions between commonly used biocides and VMPs administered via drinking water should be assessed and appropriate guidance regarding interactions and incompatibilities should be provided in the product information."

At the February 2021 CVMP meeting it was agreed to ask QWP to develop guidance to address the concerns raised by the expert group relating to the use of biocides.

3. Discussion (on the problem statement)

The quality of water used to prepare medicated water is an important aspect for the efficacy of the treatment.

At some farms, water is not supplied from the tap, but from drills or wells. Given the potential for microbial contamination, it is common practice that the water from such sources is disinfected. Chemical disinfection is carried out using biocidal products (Regulation (EU) 528/2012 type 5 products)[(4)] to reduce microbial contamination and to avoid the formation of biofilms in pipes. In many countries, potable water is also treated with biocides although this varies depending on the country/area.

Studies show that some antibiotics are subject to degradation in the presence of biocides [5] [6] [7] [8] [9] [10] [11]. Furthermore, active substances sensitive to oxidation can be degraded by biocides such as hydrogen peroxide and active chlorine [12].

This degradation could decrease the nominal dose and, as a consequence, lead to lack of efficacy and/or an increased risk of resistance development. However, compatibility of the medicated water with biocides is not currently addressed in the guideline on Quality aspects of pharmaceutical veterinary medicines for administration via drinking water and there is no EU guidance available to industry, assessors or product users to address this potential for interaction.

The impact of the presence of biocides in the water used to prepare medicated water should be considered during the development and authorisation of the relevant medicinal products. Product specific studies demonstrating compatibility with commonly used biocides should be conducted during the pharmaceutical development of new products for administration via drinking water, unless otherwise justified.

This concept paper aims to introduce the assessment of the effect of the use of biocides into the current guideline.

4. Recommendation

In order to give appropriate guidance in the SPC on the compatibility of a medicated solution in the presence of biocides, the Quality Working Party recommends the drafting of a new annex to the current guideline on Quality Aspects of Pharmaceutical Veterinary Medicines for administration via drinking water regarding assessment of interactions between Veterinary Medicinal Products and biocides. It is recommended that the annex should include guidance on the testing to be conducted to establish compatibility of the product with commonly used biocides and appropriate statements to be included in the SPC.

5. Proposed timetable

November 2021 – discussion and adoption of the Concept Paper by the QWP

January 2022 – adoption of the Concept Paper by the CVMP

February 2022 - release the Concept Paper for a 3-month consultation

It is anticipated that the draft Annex could be available within 6 months after adoption of the Concept Paper by the CVMP. The draft Annex would then be released for external consultation for 6 months before its finalisation within another 6 months. It is expected that the Annex will come into operation 6 months after adoption.

6. Resource requirements for preparation

The revision will involve the EMA-QWP Secretariat, the Joint CHMP/CVMP Quality Working Party and the CVMP. The QWP should appoint rapporteur and drafting group.

7. Impact assessment (anticipated)

It is anticipated that the guidance will lead to better awareness and improved knowledge regarding compatibility issues between Veterinary Medicinal Products and biocides and allow for appropriate information for the user to be included in the SPC's of products administered via drinking water.

8. Interested parties

Pharmaceutical industry, EU competent authorities and veterinary professionals.

9. References to literature, guidelines, etc.

(1) Letter from European Commission to EMA: Implementing measures under Article Art 106(6) of Regulation (EU) 2019/6 on veterinary medicinal products regarding rules on oral administration

(2) Guideline on quality aspects of pharmaceutical veterinary medicines for administration via drinking water-EMEA/CVMP/540/03-Rev 1 (2005)

(3) Advice on implementing measures under Article 106 (6) of Regulation (EU) 2019/6 on veterinary medicinal products – scientific problem analysis and recommendations to ensure a safe and efficient administration of oral veterinary medicinal products via routes other than medicated feed – EMA/CVMP/508559/2019 – 20 August 2020 –Committee for Medicinal Products for Veterinary Use

(4) 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

(5) CABALE: impact of treatment by biocides of drinking waters for pigs, poultry and rabbits on stability of antibiotics. P. Guichard, A. Bordas, T. Moréac, A. Chevance, J. Blot, A. Travel, A. Hémonic, B. Lenormand, M. Liber, J. Léorat, J. Verdon, D. Hurtaud-Pessel, J.-P. Orand, H. Amar, P. Maris, L. Baduel, S. Mompelat -ISSN: 0399-2519

(6) Tratamiento Antibiotico en agua de bebida y potabilizadores quimicos –J. Eulogio Pérez S.P. Veterinaria SA - https://1library.co/document/zxxwwmnz-alteracion-de-la-eficacia-del-tratamiento-antibiotico-en-agua-de-bebida-en-presencia-de-higienizantes.html#fulltext-content

(7) ANTIBI'eau : Stability of antibiotics in presence of biocides in drinking waters for pigs – A. Hémonic, P. Pupin, C. Jacob, J. Léorat, P. Maris, I. Corrégé- ISSN: 0767-9874

(8) Certains biocides altèrent la stabilité des antibiotiques- J. Léorat – Chêne Vert Conseil –Filières avicoles – Octobre 2013
http://www.chenevertconseil.com/media/fa_n768_certains_biocides_alterent_la_stabilite_des_antibio__025370800_1149_14082014.pdf

(9) Transformation of pharmaceuticals during oxidation/disinfection processes in drinking water treatment – Cristina Postigo, Susan D. Richardson -Journal of Hazardous Materials 279 (2014) 461–475doi:10.1016/j.jhazmat.2014.07.029

(10) Oxidation of pharmaceuticals by chlorine dioxide in biologically treated wastewater –G. Hey, R. Grabic, A. Ledin, J. la Cour Jansen, H.R. Andersen - Chemical Engineering Journal 185– 186 (2012) 236– 242 doi:10.1016/j.cej.2012.01.093

(11) Oxidation of sulphonamides, macrolides, and carbadox with free chlorine and monochloramine – E. Chamberlain, C. Adams - WATER RESEARCH 40 (2006) 2517 – 2526 – doi:10.1016/j.watres.2006.04.039

(12) Investigating the chlorination of acidic pharmaceuticals and by-product formation aided by experimental design methodology. Quintana JB et al. Water Research, 2010, 44, 243-255