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Committee for Veterinary Medicinal Products (CVMP)

Questions and answers on the guideline on the SPC for VMPs containing antimicrobial substances – antibiotic clinical breakpoints that may be included in section 4.2 of the SPC for generic VMPs

This Q&A follows the recent revision of the Guideline on the SPC for VMPs containing antimicrobial substances and the Quality of Review Document template (version 9)[2]. It is intended to aid the editing or update of section 4.2 of the SPC as regards antibiotic clinical breakpoints that may be included for generic VMPs.

Background:

The guideline on the summary of product characteristics for VMPs containing antimicrobial substances ('antimicrobial SPC guideline', EMA/CVMP/383441/2005-Rev.1)[3] states in section 4.2 Pharmacodynamics:

"Clinical breakpoint(s) and MICs (µg/ml) relevant for the target animal species and approved indications, if available, should be used to categorise isolates as susceptible (S), intermediate (I) or resistant (R). The reference and the year of issue for the clinical breakpoint(s) used should be given."

Question 1: Is it a requirement of the guideline to include clinical breakpoints in the SPC for generic antibiotic VMPs?

Answer: The requirements for the SPC for generic VMPs are not explicitly defined in the guideline. However, it is a requirement of Annex II to Regulation (EU) 2019/6[4] to provide information about the level of resistance, based on bibliographic data, for applications for generic antimicrobial VMPs. Therefore, if the available information includes satisfactory data relating to clinical breakpoints (see Q.2), it is desirable that this would be included in the SPC if it could assist responsible use (see details in the Rationale section).

[1] Editorial correction to Rationale: Ad Question 1, paragraph 1
[2] QRD-veterinary-product-information-annotated-template [Version 9, 03/2022] corr. 11/2022 - https://www.ema.europa.eu/en/veterinary-regulatory/marketing-authorisation/product-information/veterinary-product-information-templates
[3] Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances - https://www.ema.europa.eu/en/guideline-summary-product-characteristics-spc-veterinary-medicinal-products-containing-antimicrobial
[4] Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council (EU) (as amended by Commission Delegated Regulation (EU) 2021/805)

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Question 2: What type of clinical breakpoints could be included in the SPC for generic antibiotic VMPs?

Answer: For SPCs for generic VMPs, the AWP recommends including clinical breakpoints (CBPs) that have been established and validated for veterinary medicine, only.

The CBPs should preferably be European breakpoints (e.g. those established by the EUCAST[5] Veterinary Subcommittee on Antimicrobial Susceptibility Testing, VetCAST). If European breakpoints are not available, then international CBPs (e.g. Clinical and Laboratory Standards Institute, CLSI) could also be mentioned, according to the provisions in the Rationale below.

According to the antimicrobial SPC guideline, the CBPs should be 'relevant', that is: CBPs should be established for the target animal species as well as for the clinical condition and the target bacteria mentioned in the indications.

The most up to date CBP should be used by preference, although also taking account of the points above.

The CBP should be valid for the active substance. If no CBP is available for the active substance, a CBP for an acknowledged representative substance could be mentioned instead (see details in the Rationale section).

If no suitable CBP is available at all, information on CBPs should be omitted.

Question 3: How should the information be presented in the SPC?

Information on clinical breakpoints should be presented as follows, if available:

Clinical breakpoints established by <reference> in <year of issue> for <active substance> in <target animal> for <indication>; <organism(s)>: S: <xy> µg/ml; I: <xy> µg/ml; R: <xy> µg/ml.

This information can be presented in text or in a table (see example in the Rationale section).

Rationale:

Ad Question 1:

The scope of the guideline on the summary of product characteristics for VMPs containing antimicrobial substances applies to new marketing authorisation applications (where appropriate, depending on the legal basis of the application as defined in Regulation (EU) 2019/6) and re-examinations (Articles 24 and 27). It also applies to referrals and variation applications that require a reconsideration of the overall benefit-risk balance: for such procedures, it applies only to those parts of the SPC that fall within the direct scope of the procedure.

The requirements for the SPC for generic VMPs are not explicitly defined in the guideline. However, Annex II to Regulation (EU) 2019/6, Section IV Requirements for specific marketing authorisation applications; IV.1. Applications for generic veterinary medicinal products IV.1.3 states:

For a generic veterinary medicinal product application containing an antimicrobial substance, information about the level of resistance, as known from bibliographic data, shall be provided.

Clinical resistance is determined by CBPs. It would be meaningful and consistent to use the same type of clinical breakpoints that have been recommended in the answer to Question 2.

[5] EUCAST – European Committee on Antimicrobial Susceptibility Testing

As the dossier requirements for applications for generic VMPs are limited to provision of bibliographic data, there may be cases when CBPs cannot be provided in the SPC.

Microbiological resistance can be determined by epidemiological cut-off values (ECOFFs). However, ECOFFs are not relevant for the purpose of this Q&A.

Ad Question 2:

Clinical breakpoints define a micro-organism (i) as clinically susceptible (S) by a level of antimicrobial activity associated with a high likelihood of therapeutic success using a standard dosing regimen of the agent, (ii) as intermediate (susceptible, increased exposure 6) (I) when there is a high likelihood of therapeutic success if exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection, and (iii) as resistant (R) when there is a high likelihood of therapeutic failure even when there is increased exposure.

The request for inclusion of clinical breakpoints in the SPC is of particular relevance for the veterinarian with regard to new active substances, or known substances not previously authorised as VMPs, for which no or only minimal information is available in the public domain on how to interpret MIC data in regard to clinical susceptibility of target pathogens.

Clinical breakpoints that have been specifically validated for veterinary medicine should be included in the SPC. The development of these clinical breakpoints should follow precisely defined procedures in the sense of a standard operating procedure, which includes also the development of quality control (QC)-ranges for standardised quality control strains. The establishing institution should regularly monitor and update their breakpoints.

The gold standard for susceptibility testing of bacterial isolates is the broth microdilution method, which is performed according to the specifications of the appropriate standard method. It is important that CBPs correspond appropriately to the method used for MIC determination. It is not good practice to 'mix and match' testing methodologies and breakpoints issued by different organisations. Due to these methodological reasons and the potential lack of comparability of susceptibility results between member states, national breakpoints should not be included in the SPC.

To ensure comparability, veterinary clinical breakpoints preferably harmonised in Europe should be used. European Committee on Antimicrobial Susceptibility Testing (EUCAST) offers harmonised CBPs on a European basis to evaluate resistance data, but currently exclusively for human medicine. These CBPs are bacterial species specific and contain both CBPs for microdilution and for disc diffusion testing. Although VetCAST has been established within EUCAST, to date no veterinary clinical breakpoints have been published.

In the USA veterinary clinical breakpoints have been developed by the CLSI according to defined standards, but the data basis (e.g. dosing regimens) is not necessarily directed to European conditions. CLSI provides CBPs that are specific to animal species, bacterial species, and body sites. As for EUCAST, CLSI CBPs are available for microdilution and for disc diffusion testing. Provided that underlying dosing regimens of veterinary CLSI CBPs fit to European authorisations, they can be used as an alternative until there are harmonised European CBPs available e.g. from VetCAST.

Due to the similar in vitro activities of some antibiotics belonging to the same class, a representative antibiotic can be tested to predict susceptibility to other class members (e.g. ampicillin and tetracycline

[6] Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection. https://www.eucast.org/newsiandr

are the class representatives for aminopenicillin or tetracyclines, respectively). Use of surrogate substances should be recommended by the institution that has published the CBPs.

As regards the use of interpretative criteria for products intended only for local antimicrobial action (topical, oral with local action in the gastrointestinal tract), EUCAST has stated the following: 'It is frequently assumed that concentrations of free agent are high at the infection site, but for most topical agents it is not known what the concentrations are, how long they are maintained or what variation there is in practice. In addition, for most agents there are no sound pharmacokinetic data and no data relating treatment to outcome other than anecdotal comments. EUCAST concludes that is not possible to reach a consensus that resolves the conflicting opinions on two alternative proposals: either to use ECOFFs[7] for all agents when used topically or to use clinical breakpoints when available and ECOFFs when there are no clinical breakpoints.'

CLSI makes no recommendation regarding the gathering and evaluation of resistance data for use of topical products.

In line with that, AWP currently cannot make any recommendation on the applicability and relevance of CBPs for antibiotic VMPs used locally.

In the absence of veterinary clinical breakpoints, some laboratories use human-derived breakpoints. However, for the purpose of inclusion into SPCs for generic antibiotics, human-derived breakpoints are not considered pertinent since these breakpoints have been established based on human data (e.g. dosing regimens and pharmacokinetics). Thus, unless data are available to substantiate extrapolation from humans to animals, human-derived breakpoints cannot be considered relevant for target animal species as required according to the SPC guideline.

Ad Question 3:

Example:

Clinical breakpoints established by CLSI[8] in 2020 for florfenicol in cattle for bovine respiratory disease are as follows:

Organism	Minimum inhibitory concentration breakpoints of florfenicol (µg/ml)		
	susceptible	intermediate	resistant
Mannheimia haemolytica	≤2	4	≥8
Pasteurella multocida	≤2	4	≥8

[7] * (ECOFFS) Epidemiological cut-off values: define a micro-organism as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question or as non-wild type (NWT) for a species by the presence of an acquired or mutational resistance mechanism to the drug in question. WT and NWT micro-organisms may or may not respond clinically to antimicrobial treatment (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_SOPs/EUCAST_definitions_of_clinical_breakpoints_and_ECOFFs.pdf).

[8] CLSI. Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals: 5th ed. CLSI supplement Vet01S Clinical and Laboratory Standards Institute