Divergent position on a CVMP opinion on an Article 35 of Directive 2001/82/EC for

Veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to cattle and pigs (EMEA/V/A/117)

We, the undersigned, have a divergent position on the outcome for the Article 35 procedure for veterinary medicinal products containing gentamicin presented as solutions for injection to be administered to cattle and pigs. The divergent position concerns the withdrawal periods.

1) The model proposed for the „pragmatic procedure“ for derivation of the withdrawal period for the new dosing based on the pharmacokinetics using the terminal half-life has not been properly validated and all preconditions which must be met in order to apply this model have not been defined. As a result, the CVMP should not use the procedure until it is fully validated and preconditions for its use are properly defined. The use in this procedure might also set a precedent for a range of other cases.

2) Terminal half-life has been calculated as a mean value derived from two depletion studies and it combines two terminal half-lives calculated from the liver and one terminal half-life calculated for the kidney. This cannot be accepted as depletion from different tissues shows distinct characteristics and consequently it is not appropriate to combine different tissues to derive a single terminal half-life for the purpose of calculation of the withdrawal period from different tissues. This may be particularly relevant to substances like aminoglycosides due to their affinity and accumulation in certain tissues.

3) Terminal half-life has been calculated from the results of two depletion studies. Some data from these studies used in the calculation of the half-life were above the range of validation of the analytical method and accuracy and precision of the data has not been confirmed.

4) Based on the data available, at some early time points used for calculation of the terminal half-life, residues were identified at the injection site(s) which indicates that the absorption phase has not been completed at the respective time point points. This may affect the validity of the half-life calculated and imply that one of the basic preconditions for the use of the model has not been satisfied.

5) According to the literature (e.g. Basic Pharmacokinetics and Pharmacodynamics – An Integrated Textbook and Computer Simulations, edited by Sara E. Rosenbaum, p. 281), the aminoglycosides show non-linear pharmacokinetics, as their clearance may decrease with the dose due to the dose dependent renal toxicity. This fact renders the use of the proposed model invalid for aminoglycosides.

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