REGULATORY ASPECTS IN THE EU REGARDING ANTIMICROBIAL RESISTANCE IN VETERINARY MEDICINAL PRODUCTS AND FEED ADDITIVES

Beate Lohr, Bill Vandaele and Klaus Hellmann
Klifovet AG, Munich, Germany

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Introduction

The problem of antimicrobial resistance is related to the use of antibiotic veterinary medicinal products as well as to the use of certain additives in feed, either as bacterial strains (probiotics) or as substances exerting antimicrobial activity. Food-producing animals may contribute to human exposure to antimicrobial resistant microorganisms via consumption of contaminated meat or via contamination of water or vegetables by animal excreta. Therefore antimicrobial resistance is covered in the relevant European legislation for both, Veterinary Medicinal Products (VMPs) as well as for Feed Additives (FAs):

Veterinary Medicinal Products

Legal Background

Directive 2001/82/EC on the Community code relating to medicinal products for veterinary use, as amended by Directive 2004/28/EC and by Directive 2009/9/EC

Definitions

VMPs with antimicrobial activity are used for the treatment or prevention of bacterial diseases;
Antimicrobials = naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of other micro-organisms)[1]

Chemical structure and antimicrobial class

Mechanism and type of antimicrobial action

Consumer safety
Potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern[1]

Antimicrobial spectrum of activity
MIC (Minimal Inhibitory Concentration)-Tests, especially of food-borne pathogens and commensal organisms on recent isolates from the target animal species

Antimicrobial resistance mechanisms and genetics

Occurrence and rate of transfer of antimicrobial resistance genes

Occurrence of cross-resistance

Occurrence of co-resistance

Pharmacokinetic data to evaluate antimicrobial activity in the intestinal tract

Pharmacology
Pharmacodynamics/ Pharmakokinetics

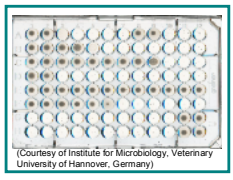
Efficacy
Therapeutic efficacy using a therapeutic regimen that aims to minimize the risk of selecting antimicrobial resistant bacteria[2]

PK-PD analysis
best relation between clinical cure and bacterial killing

Resistance mechanisms

MIC distribution of recent isolates of target pathogens
- strains from different EU regions
- not older than 5 years
- epidemiologically unrelated
- data on origin

Breakpoints for the specific target pathogens


(Courtesy of Institute for Microbiology, Veterinary University of Hannover, Germany)

Feed Additives

Legal Background

Regulation (EC) No 1831/2003 on additives for use in animal nutrition and Regulation (EC) No 429/2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003

Definitions

FAs = Substances, micro-organisms or preparations, which are intentionally added to feed or water in order to perform one or more particular functions, e.g. zootechnical effects;
Antimicrobials = substances produced either synthetically or naturally, used to kill or inhibit the growth of micro-organisms;
Antibiotic = antimicrobials produced by, or derived from a micro-organism, which destroys or inhibits the growth of other micro-organisms

QPS= Qualified Presumption of Safety[3]
Generic risk assessment system and general safety status for defined taxonomic groups of bacteria without safety concerns

Safety
In relation to animals and humans with respect to the selection and spread of antimicrobial resistance genes

Assessment of bacterial resistance[4]
Microbiological ("epidemiological") breakpoints for common bacterial species used as FA against defined antimicrobials to maximise the identification of resistance genotypes

Antimicrobial activity of an active substance at feed concentration level and MIC against relevant bacteria for the target species including zoonotic species
Antimicrobial acitivity = MIC is equal to or below four times the maximum concentration of the antimicrobial in feed/water

Microbial Studies[5]

Production of antibiotics of relevance to human or veterinary medicine

Induction of cross-resistance to antibiotics used in human or veterinary medicine

Effects on the gut microbiota of the target animal

Consequences

Antibiotics have to be authorised as VMPs in order to cure bacterial diseases. Measures to limit resistance development have to be proposed and surveillance is mandatory in each member state of EU and many countries in the world. On contrast, for FAs the use of antibiotics other than coccidiostats or histomonostats is not allowed. If a FA however shows antimicrobial activity, it has to be shown that no resistant bacterial strains are selected by its use and that there is no induction of cross-resistance with relevant antibiotics. Strains of micro-organisms carrying an acquired resistance to antimicrobials cannot be used as FAs.

References

[1] VICH GL 27: Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL)
[2] Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01-final)
[3] Scientific Opinion of the Panel on Biological Hazards on a request from EFSA on the maintenance of the QPS list of microorganisms intentionally added to food or feed. *The EFSA Journal* (2008) 923, 1-48
[4] Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) on the update of the criteria used in the assessment of bacterial resistance to antibiotics of human or veterinary importance. *The EFSA Journal* (2008) 732, 1-15
[5] EFSA Technical Guidance Microbial Studies. *The EFSA Journal* (2008) 836, 1-3