

VETERINARY PRODUCTS COMMITTEE WORKING GROUP
on
ANTIMICROBIAL RESISTANCE

Report on Antimicrobial Resistance in Relation to Veterinary Medicines

Introduction

1. During 2000/2001 the Veterinary Products Committee Working Group on Antimicrobial Resistance (see Appendix 1 for membership) considered issues relating to the licensing and use of antimicrobials that could influence the development of antimicrobial resistance (see glossary for definitions of antimicrobial and antimicrobial resistance).
2. Concerns have been raised by several international and national committees and authorities (Appendix 2) about an apparent increase in the number of resistant bacteria being identified in human medicine. The contribution, which selection of resistant bacteria in animals and their subsequent transfer to humans makes to infection of people with resistant organisms, has become a cause for concern.
3. Progress in our understanding of the mechanisms by which antimicrobials work has resulted in the development of strategies for their use that optimise their efficacy and reduce the selection for development of resistance. The licensing process should encourage the use of antimicrobials in the most effective way and strategies should be adopted which minimise the likelihood of resistance selection.
4. The Working Group has considered the use and efficacy of antimicrobials in food animals and is of the opinion that in accordance with its Terms of Reference, the report should focus on the significance of the transfer of antimicrobial resistant bacteria from food animals to humans.
5. The Working Group recognises the risk of transfer of antimicrobial resistance from companion animals to humans, and recommend that further consideration be given to the possibility of non-food animals transferring antimicrobial resistant bacteria to humans. However the group believes that there is a bigger risk posed to humans from food animals. Risks from companion animals are greatest in the family situation and are only furthered by close contact between individual owners and pets. The VPC and its Working Group are aware that far more antimicrobials are sold for use in food animals than companion animals (on a weight, rather than potency, basis) and therefore food animals are likely to have a greater potential to transfer antimicrobial resistance to humans and the environment.

Terms of Reference

6. It has been identified that use of antimicrobials in animals may contribute to the transfer of antimicrobial resistant micro-organisms found to man. The Working Group is of the opinion that given the available evidence, treatment failure in human medicine is more likely to arise from sub-optimal antimicrobial use in humans. Nevertheless, given the evidence that antimicrobial resistance may pass from animals to humans, it is appropriate and timely that the licensing process for veterinary medicines is reviewed, and that dosing regimens and strategies, which lead to optimal efficacy of antimicrobial drugs, are adopted.
7. The terms of reference of the Working Group were to 'Consider the safety and efficacy requirements for licensing antimicrobials in order to minimise the development of antimicrobial resistance and to provide guidance for industry'.
8. It was acknowledged that recommendations made by the Working Group should be harmonised with those of the Committee for Veterinary Medicinal Products (CVMP) and with the Veterinary International Committee on Harmonisation (VICH).

Background Considerations

9. Antimicrobials are essential drugs for the treatment and prevention of disease. They help to reduce animal suffering and contribute to the production of healthy livestock. The requirements for the provision of data in support of a licence claim must not be so stringent as to prevent the authorisation of potentially useful products. Nevertheless, the criteria upon which antimicrobials are licensed must be sufficiently stringent to ensure that the use of antimicrobials thus licensed minimises the selection pressure for antimicrobial resistance development.
10. Alterations to the guidelines for the submission of data in support of a licensing claim should be phased in over a period of time. A sufficiently long lead-in time is essential since the identification of appropriate dosage strategies could lead to alterations in withdrawal periods that would need to be supported by the acquisition of appropriate data.
11. Currently licensed products should be considered for review according to perceived risk associated with their generic chemical grouping. If new information becomes available which suggests that a product is being used with an inappropriate administration strategy, the licence holder will be required to submit data to justify the administration strategy or supporting data for an alternative administration strategy, including data justifying an appropriate withdrawal period. For existing products it is recommended that a review of generic chemical groups will be necessary where guidelines are changed.
12. For all products, the appropriate authorities retain the right to withdraw a marketing authorisation where new information raising concerns over the safety of the product becomes available. New information concerning the numbers of

relevant sentinel or zoonotic organisms resistant to the antimicrobial concerned should be considered with respect to the risk to the consumer (see below).

Antimicrobial Classification

13. Given the concerns raised by expert groups (Appendix 2) on the therapeutic and prophylactic use of antimicrobials in livestock it is recommended that all such use should be restricted under veterinary control. Consequently, all antimicrobials licensed for therapeutic and prophylactic use in livestock should be prescription only medicines (POMs).
14. It is noted that antimicrobials used as coccidiostats or for growth-enhancing purposes are authorised under European Regulations (70/524 EEC) and are classified as feed additives. The Working Group is of the opinion that coccidiostats are used solely for the treatment or prevention of disease in animals and should therefore be authorised as veterinary medicinal products under EU Legislation 2001/82/EEC.
15. The potential for development of cross-resistance in veterinary pathogens associated with use of growth-enhancers with antimicrobial activity needs to be considered.

Pharmacokinetic-Pharmacodynamic (PK/PD) Studies

16. Data should be provided for the antimicrobial under test to demonstrate whether dose v. time distribution results in a time-dependent activity, a concentration-dependent activity or co-dependence for concentration and time.
 - Time-dependent antimicrobials are those for which efficacy is dependent upon the period of time during which the concentration of the drug exceeds the minimum inhibitory concentration (MIC_{90}) but for which concentrations of several multiples of the MIC_{90} do not tend to result in an increase of efficacy.
 - Concentration-dependent antimicrobials are those that demonstrate increased efficacy when administered at doses that confer concentrations of several multiples of the MIC_{90} of the target organism.
 - Co-dependent antimicrobials are those for which efficacy depends upon concentrations above the MIC_{90} and a period of time during which the concentration of the drug exceeds the MIC_{90} . Either factor may dominate in importance, but both are important for establishing efficacy.
17. Currently, the most appropriate PK/PD surrogate markers in plasma to test concentration and time dependency are maximum plasma concentration (C_{max})/ MIC_{90} , time (T)> MIC_{90} and area under the concentration time curve AUC/MIC_{90} by convention referred to as AUIC or area under the inhibitory concentration time curve.
 - It is recognised that MIC_{90} is the current working standard when evaluating new antimicrobials and this has been accepted as a basis for this report. Studies to produce the MIC data should have been carried out on a representative sample of bacterial strains and using approved methods. For

substances with bactericidal activity, minimum bactericidal concentrations (MBCs) or estimates of them in relation to MICs should also be presented.

18. It may be more appropriate to use tissue or other biological fluid concentrations in PK/PD studies but this should be justified by the applicant with reference to the site of infection of the target pathogen. Because for most antimicrobials, it is generally accepted that only free drug has antibacterial activity, the proportion of the drug binding to plasma or tissue proteins should be investigated.
19. It may be possible to differentiate concentration and time dependency by reference to bacterial kill in animal models given treatment strategies as a single or number of administrations conferring the same overall dosage. This strategy is robust but does not fully differentiate absolute concentration and drug exposure when the AUC by each strategy is different. Consequently, it may be necessary to administer a single large bolus and compare this with the same dose given by infusion or by another appropriate form of administration to confer a different C_{max} or T > MIC.
20. For drugs where time and concentration dependency have been differentiated, it should be possible to titrate towards an optimum dose using a range of administration doses within the appropriate strategic routine i.e. either generating high concentration or prolonged concentrations above MIC. Where drugs have dependency towards time and concentration, AUC may be an appropriate marker to use in titration.
21. During PK/PD studies, target and sentinel bacteria (for example *Escherichia coli*, *Enterococcus faecium*) should be studied and MIC data obtained throughout the course of the different dosing strategies in order that changes in MIC, which reflect selection of resistance, can be determined.
22. The Working Group clearly recognises that information generated for specific groups of antimicrobials could be translated to other members of the group and would not wish legislation to be so restrictive that specific studies be carried out for all individual antimicrobial substances. Rather, they believe that where information can be extrapolated across a generic class of antimicrobials this should be accepted by the appropriate regulatory authorities.

Resistance Development and Post Marketing Surveillance

23. A robust system for accounting and audit of active ingredient, formulation, tonnage (relative potency), concentration, usage and target species should be developed and maintained to provide data which will be essential for the formulation of risk assessments and the ongoing interpretation and assessment of results of surveillance work.
24. The development of resistance by target bacteria, potentially zoonotic bacteria and sentinel bacteria, should be determined during pre-authorisation studies. Data should be generated *in vitro* and *in vivo* indicating the rate of development of resistance following exposure to simulated and actual treatment strategies. It is

anticipated that much of the data could be generated during the efficacy studies recommended under the current guidelines for applications for marketing authorisations.

25. The overall impact of an antimicrobial on resistance development and potential transfer into the human food chain should be estimated by post-marketing surveillance of resistance. It is recommended that a post-marketing antimicrobial resistance surveillance monitoring scheme is established which is independent and transparent. The scheme should utilise sentinel bacteria and methodology harmonised throughout the European Union. It is recommended that surveillance should be undertaken on samples collected at abattoirs since this is the point at which risk associated with husbandry systems stops and risk associated with food processing and handling begins. Sampling strategies should adhere to standard epidemiological and statistical techniques with regard to design and size.
26. The Working Group acknowledges that surveillance schemes might have an impact on the quality of meat product produced and sold within the UK. Protection of the UK consumer will only occur if the same requirements are placed on imported meat and meat products. This will enhance consumer protection within the UK and the Group strongly recommends that this be considered.
27. It is recommended that four sentinel bacteria be used for surveillance purposes and that these bacteria be utilised where it is practically possible during the pre-authorisation resistance assessment. The two zoonotic bacteria *Salmonella enterica* (serovars appropriate to the target animal(s)) and *Campylobacter* spp. should be sought whilst the two commensals *Escherichia coli* and *Enterococcus faecium* should be routinely tested. These organisms should be utilised by authorities throughout the EU.
28. Information derived from post-marketing surveillance resistance monitoring should be utilised in an overall risk assessment for an antimicrobial product that should be considered at renewal or review. It is acknowledged that data generated from post-marketing antimicrobial surveillance may be appropriately used for risk management and may assist by indicating how husbandry systems could be altered to reduce risk. The level of acceptable risk has not been defined but the VPC, VMD, Defra, FSA and DoH should work together in trying to determine the acceptable level of risk.

Antimicrobial Categories

29. Several authorities have considered antimicrobials used in humans and animals and have allocated antimicrobials for use in animals into categories according to their importance in human medicine. The underlying principle is that where 'essential' drugs are needed and where there are no alternatives in human medicine, the more stringent should be the licensing authorisation for animals, particularly where restricted posology in the authorisation may reduce the likelihood of resistance transfer to humans.

30. The Working Group considers that special consideration should be given to licensing a drug in animals that is recognised as essential for the treatment of a serious or life-threatening disease in humans for which there is no alternative, or where a drug is a member of a class of drugs that may cause cross-resistance to agents essential for human therapy.

Recommendations to Take Forward

31. Therapeutic and prophylactic use of antimicrobials in livestock should be restricted under veterinary control and should therefore be considered as prescription only medicines (POMs).

32. Coccidiostats should be authorised under EU Legislation 2001/82/EEC and should be considered as licensable under the Marketing Authorisations Regulations 1994. The VMD should make representation to the EU authorities with regard to the necessity for some oral therapeutic products, which are only going to be administered in feedingstuffs, to be of pharmaceutical quality. Exemptions should be considered for these products, on the basis of fitness for purpose.

33. Drugs essential for the treatment of a serious or life-threatening disease in humans for which there is no alternative, or where the drug is a member of a class of drugs that may cause cross-resistance to agents essential for human therapy, should be authorised with special consideration by the licensing authorities for use in animals

34. Data should be provided for the antimicrobial under test to demonstrate whether dose v time distribution results in a time-dependent activity, a concentration-dependent activity or a co-dependence for concentration and time.

35. Where guidelines are changed, a review of generic chemical groups should be undertaken to include existing products as well as new products.

36. Alterations to the guidelines for the submission of data in support of a licensing claim should be phased in over a period of time as identification of appropriate dosage strategies could lead to alterations in withdrawal periods that would require acquisition of appropriate data.

37. A post marketing antimicrobial resistance-monitoring scheme should be established, which is independent and transparent. Surveillance should be undertaken on UK samples collected at abattoirs and be extended to imported meat and meat products.

38. Four sentinel bacteria should be used for surveillance purposes and these organisms should be utilised where it is practically possible during the pre-authorisation resistance assessment. These organisms should be agreed standards throughout the EU.

39. The VPC, VMD, Defra, FSA and DoH should work together to determine the acceptable level of risk of development of antimicrobial resistance.
40. The potential for development in veterinary pathogens of cross-resistance to antimicrobials used therapeutically in humans and in veterinary species associated with the use of antimicrobial growth enhancers needs to be considered.
41. Because of lack of data further consideration should be given to the possibility of non-food animals transferring antimicrobial resistant bacteria to humans. Nevertheless, during the authorisation process, attention should be given to appropriate usage guidelines, including personal hygiene. The Working Group support and commend Government recommendations on prudent use guidelines and continued education of veterinary surgeons and the medical profession.

Glossary

Antibiotic	a substance produced by, or derived from a micro-organism which selectively destroys or inhibits the growth of other micro-organisms.
Antimicrobial agent	a compound which, at low concentrations, exerts an action against micro-organisms and exhibits selective toxicity towards them.
Antimicrobial resistance	is the ability of a micro-organism to withstand an antibiotic.
Bactericidal	an antimicrobial that is able to kill bacteria (e.g. β -lactams, aminoglycosides).
Coccidiostat	a product that controls coccidiosis (a protozoal disease which can cause diarrhoea and dysentery). Control of this infection is especially important in the poultry industry where the prophylactic use of coccidiostats prevents disease from developing.
Concentration dependency	concentration-dependent antimicrobials are those that demonstrate increased efficacy when administered at doses which confer concentrations several fold higher than the MIC ₉₀ of the target organism.
Growth promoters	antimicrobials used at low concentrations to stimulate an animal's growth, resulting in increased daily live weight gain and feed conversion efficiency.
MIC	minimum inhibitory concentration; the lowest concentration of an antimicrobial that inhibits the growth of a defined number of bacteria, under defined conditions and duration of culture.
MBC	minimum bactericidal concentration; the lowest concentration of an antimicrobial able to produce complete killing of a defined number of bacteria, in defined media and within a defined time.
Prophylaxis	the administration of antimicrobials in advance of symptomatic disease.
Therapy	the treatment of disorders or disease.
Time dependency	time-dependent antimicrobials are those for which efficacy is dependent upon the period of time during which the concentration of the drug exceeds the MIC ₉₀ .

Membership of the Veterinary Products Committee *ad hoc* Working Group on Antimicrobial Resistance.

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RECOMMENDATIONS IN REPORT FROM THE VETERINARY PRODUCTS COMMITTEE'S WORKING GROUP ON ANTIMICROBIAL RESISTANCE IN RELATION TO VETERINARY MEDICINES

“Therapeutic and prophylactic use of antimicrobials in livestock should be restricted under veterinary control and should therefore be considered as prescription only medicines (POMs).”

1. VMD agrees with this recommendation. All veterinary medicines with antimicrobial properties are classed as prescription only medicines in the UK. One of the key planks to the Governments strategy to reduce the amount of antibiotics used on farm is to ensure the prudent use of all medicines. The Government actively supports the Responsible Use of Medicines in Agriculture (RUMA) alliance and its published advice on prudent use of veterinary medicines.

“Coccidiostats should be authorised under EU Legislation 2001/82/EEC and should be considered as licensable under the Marketing Authorisations Regulations 1994. The VMD should make representation to the EU authorities with regard to the necessity for some oral therapeutic products, which are only going to be administered in feedingstuffs, to be of pharmaceutical quality. Exemptions should be considered for these products, on the basis of fitness for purpose.”

2. VMD agrees with this recommendation. It has made representations to the European Commission for coccidiostats to be removed from the scope of the proposed new Council Regulation on Feed Additives and included within the scope of Council Directive 2001/82/EEC. Similar representations have been made by a number of other Member States and at the European Parliament. The EU Commission has proposed that these products should remain classified as feed additives for the time being but that the Commission should be charged with reviewing their status before 1 January 2008.

“Drugs essential for the treatment of a serious or life-threatening disease in humans for which there is no alternative, or where the drug is a member of a class of drugs that may cause cross-resistance to agents essential for human therapy, should be authorised with special consideration by the licensing authorities for use in animals.”

3. VMD agrees with this recommendation. This is already applied in the assessment of a new antibiotic product for the treatment of animals.

“Data should be provided for the antimicrobial under test to demonstrate whether dose v time distribution results in a time-dependent activity, a concentration-dependent activity or a co-dependence for concentration and time.”

4. VMD agrees with this recommendation. Data that can provide this information are already required as part of the application for a Marketing Authorisation (MA).

“Where guidelines are changed, a review of generic chemical groups should be undertaken to include existing products as well as new products.”

5. VMD does not agree with this recommendation. MA holders are already required to update dossiers in line with significant changes in guidelines at the time of the renewal of their MA (i.e. every five years). The European Medicines Evaluation Agency (EMA)'s Committee on Veterinary Medicinal Products (CVMP) has recommended that such changes to guidelines should only be applied to new products, unless there is evidence that there is a problem with existing products, for example through pharmacovigilance. VMD agrees with this position. It would not be legal to impose requirements on UK MA holders above those required in other Member states.

“Alterations to the guidelines for the submission of data in support of a licensing claim should be phased in over a period of time as identification of appropriate dosage strategies could lead to alterations in withdrawal periods that would require acquisition of appropriate data.”

6. VMD agrees with this recommendation. Any changes in dosages could potentially lead to residues issues. Where dosage regimes are increased this may result in the original withdrawal period being insufficient to ensure that any veterinary medicinal product residues are at or below the Maximum Residue Limit (MRL) set in EU law. In such cases new data would be required in support of a new withdrawal period.

“A post marketing antimicrobial resistance-monitoring scheme should be established, which is independent and transparent. Surveillance should be undertaken on UK samples collected at abattoirs and be extended to imported meat and meat products.”

7. VMD agrees with this recommendation. Defra's Veterinary Laboratories Agency (VLA) currently collects samples of healthy cattle, pigs and sheep destined for the food chain from abattoirs on an annual basis. This survey is designed to determine the prevalence of food borne pathogens and patterns of antimicrobial resistance in these animals. Results from these surveys provide a base line on the prevalence of *E. coli* O157, *E. coli* coliforms, *Enterococci*, *Campylobacter* spp. and *Salmonella* spp. Their findings are published annually in reports available from the VLA. The additional surveillance required under

this recommendation will be included in Defra's antimicrobial resistance surveillance strategy.

“Four sentinel bacteria should be used for surveillance purposes and these organisms should be utilised where it is practically possible during the pre-authorisation resistance assessment. These organisms should be agreed standards throughout the EU.”

8. VMD disagrees with this recommendation. Bacteria to be covered by a surveillance programme of this nature should include those bacteria that are pathogenic to animals, zoonotic organisms and commensal bacteria to produce data on risks to public health and linked with resistance as well as patterns of disease in animals. This kind of survey would also identify emerging problems of lack of efficacy in antimicrobials used to treat diseases in animals that may be used to resistance. Recent OIE Guidelines have recommended a list of bacteria that should be tested for in cattle, pigs, sheep and poultry samples. These Guidelines recommend that up to 13 bacteria should be used in surveillance in cattle and pigs, 11 in sheep and 10 in poultry.

“The VPC, VMD, Defra, FSA and DoH should work together to determine the acceptable level of risk of development of antimicrobial resistance.”

9. VMD agrees with this recommendation. The Government has several cross-departmental committees in place addressing the issue of antimicrobial resistance. The Specialist Advisory Committee on Antimicrobial Resistance (SACAR) and the Interdepartmental Steering Group on Antimicrobial Resistance (IDSG) include members from VPC, VMD, Defra, FSA and DoH, as well as others. Further Committees such as the Defra Antimicrobial Resistance Coordination (DARC) Group and the Advisory Committee on Microbiological Safety of Food (ACMSF) also address antimicrobial resistance and closely corroborate with IDSG and SACAR. These groups discuss, and where necessary, investigate further issues related to AMR and put in place systems for assessing the risks associated with those issues.

“The potential for development in veterinary pathogens of cross-resistance to antimicrobials used therapeutically in humans and in veterinary species associated with the use of antimicrobial growth enhancers needs to be considered.”

10. VMD agrees with this recommendation. The antimicrobials chosen for the surveillance programme reflect their therapeutic importance in man and animals. Some may no longer be used or available, but given that resistance may persist long after use of a particular agent, continued surveillance may provide important longer-term information on trends and understanding epidemiology. The surveillance programme should also be flexible, changing in time to reflect changes in antimicrobial availability, developments in the medical field and prescribing practices. Antimicrobials to monitor should be in line with those proposed in the recent OIE Guidelines.

“Because of lack of data further consideration should be given to the possibility of non-food animals transferring antimicrobial resistant bacteria to humans. Nevertheless, during the authorisation process, attention should be given to appropriate usage guidelines, including personal hygiene. The Working Group support and commend Government recommendations on prudent use guidelines and continued education of veterinary surgeons and the medical profession.”

11. VMD agrees with this recommendation. The DARC Group has identified that surveillance of antimicrobial resistance in companion animals, and its transfer to human, as a potential risk. However the Group also considered that surveillance of antimicrobial resistance in food producing animals, e.g. cattle, pigs, sheep, poultry, fish and game, was of a higher importance, as one food producing animal has the potential to affect many humans.

VMD agrees that it is good practice for anyone handling any animal for any purpose to take appropriate hygiene precautions. However it does not consider that it would be appropriate to include advice on this on medicines labels, as this could reduce the impact of the primary information and safety warnings relating to the products themselves.

VMD welcomes the Working Group’s support for its promotion of the guidelines on prudent use and continued education of veterinary surgeons and the medical profession.