



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Veterinary Use

EMEA/CVMP/818/99-Final

A Risk Management Strategic Plan for controlling Antimicrobial Resistance through the Authorisation of Veterinary Medicines

Recommendations consequent to the Report and Qualitative Risk Assessment of the CVMP (July 1999)

12 January 2000

1) Remit

“To develop and implement a comprehensive Risk Management Strategic Plan (RMSP) which will lead to the development of principles, guidelines and measures to ensure the authorisation of antimicrobial products for veterinary use permits effective, efficient usage, whilst guarding against the development of resistance in the human and animal populations.”

2) Scope of the plan

- a) The recommendations contained in the CVMP report entitled “Antibiotic resistance in the European Union Associated with therapeutic use of Veterinary Medicines” will form the basis for the RMSP. In addition, other reports available dealing with antibiotic resistance (see Appendix 1) should also be taken into account.
- b) Creating links with groups developing initiatives for human antimicrobials will also be essential, including CPMP activities as well as national initiatives. Some examples of guidelines from the CPMP, which may be relevant, are referenced in Appendix II. Continued liaison with the European Commission will also be important to consider the recommendations contained in the opinion of Scientific Steering Committee on Antimicrobial Resistance (see Appendix I).
- c) The need for specific guidelines detailing the requirements for the authorisation of new antimicrobials and for updating knowledge on existing antimicrobials is emphasised. These should include pre-authorisation sensitivity testing and post marketing surveillance.
- d) Development of public and professional information intended to alert users of antimicrobials of the correct, prudent and effective use of these products. In addition, how to impart a consistent message through the medium of the Summary of Product Characteristics should be examined.
- e) How surveillance data may be used to modify or inform the regulatory process. How surveillance will be organised and what type of information will be of most use in the regulatory process.
- f) How Minimum Inhibitory Confirmation (MIC) breakpoints and pharmacodynamic and pharmacokinetic data may be used to assure the selection of effective doses and treatment programs. A consistent approach across Member States, in compliance with Community legislation, is essential.
- g) Antibiotic groups for which special considerations may be necessary.
- h) Identification of bacterial diseases and husbandry systems that would benefit from an improved approach to prophylaxis (e.g. through hygiene measures, health schemes, eradication policies and encouragement of the use of vaccines).
- i) The role of antibacterial prophylaxis in the treatment of herds and flocks should be closely examined.
- j) Consideration of the available legislation and its ability to assist the proposed strategy. In addition, Article 70 of Council Regulation 2309/93 EEC states: “Within three years of the entry into force of this regulation the Commission shall produce a report on whether the level of harmonisation achieved by this Regulation and by Council Directive 90/167/EEC of 26 March 1990 laying down conditions governing the preparation, placing on the market and use of medicated feeding stuffs in the Community is equivalent to that provided for in Council Directive 70/524/EEC, accompanied if necessary by the proposals to modify the status of the coccidiostats and other medicinal substances covered by that Directive.”

There are some areas that do not clearly fall under the remit of the CVMP but impinge upon this work:

- k) Advertising and distribution of antimicrobials.
- l) Trade imbalances with non-EU countries caused, in particular, by the pattern of use of antimicrobials outside the EU.
- m) GMO marker genes in crops (coded for antibiotic resistance).
- n) The role of antimicrobials used in agricultural production and the part this plays in the development of resistance in animals fed treated crops.

3) Defining Risk

The following definitions were accepted by CVMP in the Working Party report on Antimicrobial Resistance:

Definition of Risk management: A systematic process of defining the acceptable risk and deciding the most appropriate level of protection based on the highest possible level of consensus. (Ref Ch. VI p.60 – CVMP Report)

Definition of Risk Communication: Dialogue about risk and benefits concerning certain problems and possible measures between stakeholders. (Ref Ch. VI p.60 – CVMP Report)

4) Strategic Plan

In developing a strategic plan for the management of resistance, it is important to review the risk assessment process previously undertaken and determine what safeguards are reasonably required to manage the risk elements. In evaluating a risk assessment it should be possible to identify the direct action that can be taken. However it is recognised that the available data that would permit effective risk assessment of antimicrobial resistance is incomplete. Thus the data that would be required to allow an improvement in risk analysis should be identified with a view to conducting further risk assessment of a quantitative nature. The results would in turn permit modification of risk management through better risk assessment.

Finally, it is necessary to discuss the communication of any agreed Risk Management strategy to a wider audience to ensure the greatest possible consensus. The qualitative risk assessment in the CVMP report entitled "Antibiotic resistance in the European Union Associated with therapeutic use of Veterinary Medicines", identified several areas where important data was unavailable. Thus much of the assessment of risk is subject to expert view rather than numeric quantifiable fact. This must be kept in mind when planning a strategy for risk management.

A strategy for managing the risk of developing antimicrobial resistance can be divided into three areas:

- i) Ensuring effective use of antibiotics through the authorisation process.
- ii) Informing those responsible for the assessment process through the availability of useful data
- iii) External communication to promote effective and prudent use of antimicrobials products and permit co-ordinated action across traditional boundaries.

4(i) Ensuring effective use of antibiotics through the authorisation process

There are several elements to the assessment process that can address the issue of antibiotic resistance and lead to the more effective use of antimicrobial compounds. Flowing from an effective assessment process should be meaningful information, used for the SPC and product labelling to encourage the effective use of products. Thus taking advantage of any measures put in place to limit the development and spread of resistance. However, to do this the CVMP will need to develop clear guidelines on data requirements and the authorisation parameters that are critical for this strategy to work. It is also important that the effect of any intervention or initiative is measured to ensure the value and justification of regulatory actions

Listed below are the points that are directly related to the assessment process that could improve the management of resistance in veterinary medicine. The points are listed in the proposed order of importance.

- a) A critical evaluation of the data related to MIC's, drug kinetics and target bacteria/diseases (pharmacokinetic/pharmacodynamic interactions – to encompass kill curves and post antibiotic effects. Additionally, an evaluation of current relevance of using MIC and kinetic data as related to the setting of dosage levels is essential if under-dosing is to be avoided. In particular consideration should be given to the setting of MIC breakpoints for specific bacteria to permit ongoing monitoring of resistance.
- b) Guidelines are required to satisfy the modern regulatory requirements for the resistance section of Part IV of the dossier. In particular a description of the testing aimed at establishing the likelihood of resistance developing to novel antimicrobials. Guidelines should include the identification of target bacteria of importance in surveillance before and after authorisation.
- c) Guidelines for post marketing surveillance using MIC breakpoints or other methods to evaluate resistance in the field. Identify actions to be taken if breakpoints/limits are exceeded.
- d) Guidelines for the calculation of antimicrobial dosage and the risk assessment/management process required for new active ingredients.
- e) Develop policy to ensure clear, targeted claims for new and existing antimicrobials to encourage effective usage.
- f) Summary of Product Characteristics (SPC) – Use of standard phrases and formats to inform the end user. The SPC requires clearly defined posology/treatment regimes, target organisms and diseases. It should also be the case that clear contra-indications for therapeutic indications for which the treatment will not be effective or desirable are noted in the SPC.
- g) All antimicrobial products authorised via the Centralised, National and Mutual Recognition procedures should be subject to veterinary prescription.
- h) Given that resistance is driven by the volume of active used and the route of administration the CVMP should develop definitive guidelines for antimicrobial prophylaxis; combination therapies; in-feed and water mass medication.
- i) Identify infectious diseases that have a major impact on antimicrobial usage and would benefit from the development of alternative control methods (e.g. immunological products). The primary focus could be zoonotic diseases.
- j) Where new immunological products or new husbandry standards are introduced or where new risk management procedures are put in place, monitoring programs to measure their effect should be considered. Such measures might include reductions in the use/consumption of antimicrobials and the effect on the development of resistance.

4(ii) Informing the assessment process through the availability of appropriate, useful data

Gathering data to assist the risk assessment process as well as the development of strategy and regulatory policy will ultimately permit risk management to be targeted efficiently and effectively. It is therefore an important adjunct to the risk management process. The following areas require comment from the CVMP:

- a) Market surveillance data: Volume usage of antimicrobial products is currently available only through general marketing studies and is often extrapolated and subject to regional inaccuracies. More robust data is required to permit greater understanding of the key drivers in resistance selection. Species usage patterns and animal statistics are required to complement the volume usage figures to permit analysis of key areas for attention. This data needs to be collected by member states, centrally co-ordinated and analysed annually. The co-operation of the industry sector will be essential
- b) Monitoring antimicrobial resistance is carried out to different degrees across Europe. A co-ordinated approach is required to gather data effectively across Europe using agreed standard techniques in sampling, screening and measurement of resistance. Comparative data will allow trends to be analysed and related to different national conditions and practice. A recent proposal from the Centre Européen D'Etudes pour la Santé Animale on surveillance network of Zoonotic Pathogens Susceptibility (see Annex I) merits detailed consideration and consideration of national surveillance programmes will be very useful too.
- c) Resistance surveillance is expensive and should be targeted to those areas that will yield best information. Thus it is essential for the CVMP to identify the parameters it requires, detailing which species; pharmaceutical active ingredients and organisms should be targeted for surveillance. Additionally, the new molecules most likely to generate cross resistance to human products of importance should be a major focus
- d) Research into hygiene measures that will reduce the risk of contamination of human food products is outside the remit of the CVMP. However such measures on farm to limit the spread of disease and reduce antibiotic usage can be considered.

4(iii) External communication to promote effective use and co-ordinate action across traditional boundaries.

- a) Disseminate information on those diseases that would benefit from finding alternative control methods (e.g. such as vaccines).
- b) Effective exchange of information with the human medical field, to ensure co-ordinated decisions are taken on authorisation issues and surveillance.
- c) Ensure CVMP guidance is applied to the Centralised, National and Mutual Recognition procedures thus maintaining consistency across the EU (Ch. VIII p.61 – CVMP Report).
- d) Encourage clear professional guidelines for vets and doctors through the development of formularies. For example consider the USA approach to antimicrobial selection, especially for novel classes of active, special indications, pathogens and species other approaches may also be considered.
- e) Review recommendations of European Commission DGXXIV Steering Committee report (see Annex I).

5) Political questions

- a) Article 70 of Council Regulation 2309/03 EEC requires action by the Commission in relation to coccidiostats, with possible extension to include the growth promoting antimicrobials.

- b) A Directive dealing with data collection:: As the legal base for data collection is just being developed, advice should be sought from the Commission on how this will be formalised
- c) Legal Categorisation, the cascade and distribution of antimicrobials: At a time when the cascade is being reconsidered it is essential that the usage of antimicrobials be kept in mind. It may be that the use of antimicrobials under the cascade provisions should be considered separately. In any event, the legal category of the therapeutic antimicrobial products must remain under veterinary prescription.
- d) Antibiotic advertising and distribution: It has already been proposed that the legal classification of antimicrobials needs to be considered. However the controls on distribution and veterinary dispensing of antimicrobials are also potentially important factors. In addition, thought needs to be given to the advertising and promotion of these important pharmaceuticals and the appropriate standards that should be applied
- e) Trade imbalances with non-EU countries: Action on antimicrobial usage through the authorisation system in the EU will be valueless unless the community can ensure third party countries are adopting equivalent standards. How this is enforced is outside the remit of the CVMP but it is an important issue and the CVMP may be able to advise on how testing may assist in any control program.
- f) The use of GMO marker genes in crops (coded for antibiotic resistance) highlights the need for action on antimicrobial resistance to extend beyond the authorisation of human and veterinary medicines. Suitable links need to be developed throughout the EU to ensure activities are harmonised and that the use of resistance marker genes is more appropriate (e.g. mercury resistance).
- g) Ecological issues related to disposal of waste product containing antimicrobials, require consideration during the authorisation process. Additionally the increasing use of common commensal organisms as alternatives to therapeutic treatment and growth promoters raises the question of the controls on the organisms used and their ability to transmit the genetic coding for resistance to pathogens. The CVMP will need to consider how this can be best assessed.

6) Summary

The risk management strategic plan for controlling antimicrobial resistance through the authorisation of veterinary medicines can be summarised as follows:

1. Review the risk assessment process to identify the areas where direct action is possible and highlight the significant gaps in data currently available.
2. Communicate the conclusions of this review to other interested parties, especially in those areas where data deficiencies are outside the remit of the CVMP.
3. Put in place guidelines detailing the data requirements for the assessment process, to ensure the risk of antimicrobial resistance developing can be adequately defined.
4. Ensure a consistent approach, in terms of product information supplied to the end user and public, to ensure effective prudent use of antimicrobials.
5. Identify infectious diseases where immunological products or husbandry changes would have a significant impact by reducing the volume of antimicrobials used.
6. Comment on these areas where research and data collection is intended, to ensure it informs the assessments of risk and improves the management of risk through regulatory controls.

7. Communicate and co-ordinate CVMP activity with other interested parties to ensure a consistent, effective approach to the problem of antimicrobial resistance.
8. Advise the Commission of significant 'political issues' and their potential impact on the 'risk management plan' of the CVMP.

The strategy set out above is a comprehensive first step towards achieving more prudent, effective use of antimicrobials. Each item requires detailed thought, planning and a working consensus with all interested parties. The CVMP can achieve progress through those actions which lie within its remit, but success relies upon effective communication and agreement with other groups such as CPMP, the Commission, consumers and the various health based professions.

APPENDIX 1

1. CVMP's ad hoc Working Party on Antimicrobial Resistance.
2. Antimicrobial Resistance – World Health Organisation.
3. The Microbial Threat – EU Copenhagen Conference 9-10 September 1998.
4. Opinion of the Scientific Steering Committee on Antimicrobial Resistance.
5. House of Lords Scientific Select Committee Report on Resistance to Antibiotics and Other Antimicrobial Agents.
6. Antimicrobial Resistance – House of Commons Agriculture Committee Enquiry into Food Safety.
7. Advisory Committee on the Microbiological Safety of Food –Report on Microbial Antibiotic Resistance in Relation to Food Safety.
8. The Standing Medical Advisory Committee – The Path of Least Resistance.
9. A Review of Antimicrobial Resistance in the Food Chain, a Technical Report for MAFF.

APPENDIX 2

Guideline on the Evaluation of New Anti-bacterial Medicinal Products CPMP/EWP/558/95 October 1997.

Guideline on Pharmacodynamic Section of the SPC for Antibacterial Medicinal Products CPMP/EWP/502/96 December 1997.

Proposed Position Statement on Antibiotic Resistance in the EU CPMP, October 1998.