

CODE OF PRACTICE TO MINIMIZE AND CONTAIN ANTIMICROBIAL RESISTANCE
CAC/RCP 61-2005

| | |
|---|----|
| INTRODUCTION | 2 |
| AIMS AND OBJECTIVES | 2 |
| RESPONSIBILITIES OF THE REGULATORY AUTHORITIES | 4 |
| Quality Control of veterinary antimicrobial drugs | 5 |
| Assessment of efficacy | 5 |
| Assessment of the potential of veterinary antimicrobial drugs to select for resistant microorganisms | 6 |
| Establishment of ADIs (acceptable daily intake). MRLs (maximum residue limit), and Withdrawal periods for veterinary antimicrobial drugs | 6 |
| Establishment of a summary of product characteristics for each veterinary antimicrobial drug for food-producing animals | 7 |
| Surveillance programmes | 7 |
| Distribution of veterinary antimicrobial drugs in veterinary medicine | 8 |
| Control of advertising | 8 |
| Training of veterinary antimicrobial drug users | 9 |
| Development of research | 9 |
| Collection and destruction of unused veterinary antimicrobial drugs | 9 |
| RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY | 9 |
| Marketing authorisation of veterinary antimicrobial drugs for food-producing animals | 9 |
| Marketing and export of veterinary antimicrobial drugs | 10 |
| Advertising | 10 |
| Training | 10 |
| Research | 10 |
| RESPONSIBILITIES OF WHOLESALE AND RETAIL DISTRIBUTORS | 10 |
| RESPONSIBILITIES OF VETERINARIANS | 10 |
| Off-label use | 12 |
| Recording | 12 |
| Training | 12 |
| RESPONSIBILITIES OF PRODUCERS | 12 |
| CONCLUSIONS | 14 |
| Endnotes | 14 |
| List of Abbreviations | 14 |
| Glossary and Definitions of Terms | 15 |

INTRODUCTION

1. This document provides additional guidance for the responsible and prudent use of antimicrobials in food-producing animals, and should be read in conjunction with the Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993. Its objectives are to minimize the potential adverse impact on public health resulting from the use of antimicrobial agents in food-producing animals, in particular the development of antimicrobial resistance. It is also important to provide for the safe and effective use of veterinary antimicrobial drugs in veterinary medicine by maintaining their efficacy. This document defines the respective responsibilities of authorities and groups involved in the authorization, production, control, distribution and use of veterinary antimicrobials such as the national regulatory authorities, the veterinary pharmaceutical industry, veterinarians, distributors and producers of food-producing animals.

2. The marketing authorization procedure has a significant role in establishing the basis for prudent use of veterinary antimicrobial drugs in food-producing animals through clear label indications, directions and warning statements.

3. A number of codes of practice relating to the use of veterinary antimicrobial drugs and the conditions thereof have been developed by different organisations. These codes were taken into consideration and some elements were included in the elaboration of this Code of Practice to Minimize and Contain Antimicrobial Resistance.

4. In keeping with the Codex mission, this Code focuses on antimicrobial use in food-producing animals. It is recognized that antimicrobial resistance is also an ecological problem and that management of antimicrobial resistance may require addressing the persistence of resistant microorganisms in the environment. Although this issue is most relevant for CCRVDF with respect to food-producing animals, the same principles apply to companion animals, which also harbor resistant microorganisms.

AIMS AND OBJECTIVES

5. It is imperative that all who are involved in the authorisation, manufacture, sale and supply, prescription and use of antimicrobials in food-producing animals act legally, responsibly and with the utmost care in order to limit the spread of resistant microorganisms among animals so as to protect the health of consumers.

6. Antimicrobial drugs are powerful tools for the management of infectious diseases in animals and humans. This Code and existing guidelines for the responsible use of antimicrobial drugs in food-producing animals include recommendations intended to prevent or reduce the selection of antimicrobial resistant microorganisms in animals and humans in order to:

- Protect consumer health by ensuring the safety of food of animal origin intended for human consumption.
- Prevent or reduce as far as possible the direct and indirect transfer of resistant microorganisms or resistance determinants within animal populations and from food-producing animals to humans.
- Prevent the contamination of animal derived food with antimicrobial residues which exceed the established MRL.
- Comply with the ethical obligation and economic need to maintain animal health.

7. This Code does not address environmental issues related to antimicrobial resistance from the use of veterinary antimicrobial drugs but it encourages all those involved to consider the ecological aspects when implementing the Code. Efforts should be made to ensure that environmental reservoirs of veterinary antimicrobial drugs, antimicrobial resistant organisms and resistance determinants are kept to a minimum. In particular:

- Regulatory authorities should assess the impact of proposed veterinary antimicrobial drug use on the environment in accordance with national guidelines or recognized international guidelines¹
- Research should be conducted on resistant microorganisms in the environment and the magnitude of resistance determinant transfer among microorganisms in the environment.

8. The responsible use of veterinary antimicrobial drugs in food-producing animals:

- is controlled by the veterinary profession or other parties with the required expertise.
- is part of good veterinary and good animal husbandry practice and takes into consideration disease prevention practices such as the use of vaccination and improvements in husbandry conditions.
- aims to limit the use of veterinary antimicrobial drugs according to their approved and intended uses, and takes into consideration on-farm sampling and testing of isolates from food-producing animals during their production, where appropriate, and makes adjustments to treatment when problems become evident.
- should be based on the results of resistance surveillance and monitoring (microbial cultures and antimicrobial sensitivity testing), as well as clinical experience.
- does not include the use for growth promotion of veterinary antimicrobial drugs that belong to or are able to cause cross resistance to classes of antimicrobial agents used (or submitted for approval) in humans in the absence of a risk analysis. This risk analysis should:
 - be undertaken by the appropriate national regulatory authority;
 - be based on adequate scientific evidence; and
 - focus on the potential to impact resistance to antimicrobials used in human medicine.
- is aimed at all the relevant parties, such as:
 - regulatory and scientific authorities;
 - the veterinary pharmaceutical industry;
 - distributors and others handling veterinary antimicrobial drugs;
 - veterinarians, pharmacists and producers of food-producing animals.

¹ VICH (2000). Guidelines on Environmental Impact Assessment for Veterinary Medicinal Products, Phase I. http://vich.eudra.org/pdf/2000/G106_st7.pdf

RESPONSIBILITIES OF THE REGULATORY AUTHORITIES

9. The national regulatory authorities, which are responsible for granting the marketing authorisation for antimicrobials for use in food-producing animals, have a significant role in specifying the terms of this authorisation and in providing the appropriate information to the veterinarian through product labelling and/or by other means, in support of prudent use of veterinary antimicrobial drugs in food-producing animals. It is the responsibility of regulatory authorities to develop up-to-date guidelines on data requirements for evaluation of veterinary antimicrobial drug applications. National governments in cooperation with animal and public health professionals should adopt a proactive approach to promote prudent use of antimicrobials in food-producing animals as an element of a national strategy for the containment of antimicrobial resistance. Other elements of the national strategy should include good animal husbandry practices, vaccination policies and development of animal health care at the farm level, all of which should contribute to reduce the prevalence of animal disease requiring antimicrobial treatment. Use of veterinary antimicrobial drugs for growth promotion that belong to classes of antimicrobial agents used (or submitted for approval) in humans and animals should be terminated or phased out in the absence of risk-analysis, as described in Paragraph 8.

10. It is the responsibility of the pharmaceutical company or sponsor² to submit the data requested by the regulatory authorities for granting marketing authorisation.

11. The use of antimicrobial agents in food-producing animals requires a marketing authorisation, granted by the competent authorities when the criteria of safety, quality and efficacy are met.

- The examination of dossiers/drug applications should include an assessment of the risks to both animals and humans resulting from the use of antimicrobial agents in food-producing animals. The evaluation should focus on each individual veterinary antimicrobial drug but take into consideration the class of antimicrobials to which the particular active principle belongs.
- The safety evaluation should include consideration of the potential impact of the proposed use in food-producing animals on human health, including the human health impact of antimicrobial resistance developing in microorganisms found in food-producing animals and their environment associated with the use of veterinary antimicrobial drugs.

12. If dose ranges or different durations of treatment are indicated, the national authorities should give guidance on the approved product labelling regarding the conditions that will minimize the development of resistance, when this information is available.

13. The relevant authorities should make sure that all the antimicrobial agents used in food-producing animals are prescribed by a veterinarian or other suitably trained person authorized in accordance with national legislation or used under conditions stipulated in the national legislation. (See OIE Guidelines for Antimicrobial Resistance: Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine (Terrestrial Animal Health Code, Appendix 3.9.3))

14. No veterinary antimicrobial drug should be administered to animals unless it has been evaluated and authorized for such use by the relevant authorities or the use is allowed through off-label guidance or legislation. Regulatory authorities should, where possible, expedite the market approval process of new veterinary antimicrobial drug formulations considered to have the potential to make an important contribution in the control of antimicrobial resistance.

15. Countries without the necessary resources to implement an efficient authorisation procedure for veterinary antimicrobial drugs and whose supply of veterinary antimicrobial drugs mostly depends on imports from foreign countries should:

- ensure the efficacy of their administrative controls on the import of these veterinary antimicrobial drugs,

² As defined in the VICH Good Clinical Practice Guideline, http://vich.eudra.org/pdf/2000/GI09_st7.pdf

- seek information on authorizations valid in other countries, and
- develop the necessary technical cooperation with experienced authorities to check the quality of imported veterinary antimicrobial drugs as well as the validity of the recommended conditions of use. Alternatively, a national authority could delegate a competent institution to provide quality certification of veterinary antimicrobial drugs.

16. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of illegal and/or counterfeit bulk active pharmaceutical ingredients and products. Regulatory authorities of importing countries could request the pharmaceutical industry to provide quality certificates or, where feasible, certificates of Good Manufacturing Practices prepared by the exporting country's national regulatory authority.

QUALITY CONTROL OF ANTIMICROBIAL AGENTS

17. Regulatory authorities should ensure that quality controls are carried out in accordance with international guidance and in compliance with the provisions of good manufacturing practices, in particular:

- to ensure that the quality and concentration (stability) of veterinary antimicrobial drugs in the marketed dosage form(s) is maintained and properly stored up to the expiry date, established under the recommended storage conditions.
- to ensure the stability of veterinary antimicrobial drugs when they are mixed with feed or drinking water.
- to ensure that all veterinary antimicrobial drugs are manufactured to the appropriate quality and purity.

ASSESSMENT OF EFFICACY

18. Preclinical data should be generated to establish an appropriate dosage regimen necessary to ensure the efficacy of the veterinary antimicrobial drug and limit the selection of microbial resistant microorganisms. Such preclinical trials should, where applicable, include pharmacokinetic and pharmacodynamic studies to guide the development of the most appropriate dosage regimen.

19. Important pharmacodynamic information may include:

- mode of action;
- the spectrum of antimicrobial activity of the substance;
- identification of bacterial species that are naturally resistant relevant to the use of the veterinary antimicrobial drugs;
- antimicrobial minimum inhibitory and/or bactericidal concentrations;
- determination of whether the antimicrobial exhibits time or concentration-dependent activity or co-dependency,
- evaluation of activity at the site of infection.

20. Important pharmacokinetic information may include:

- bio-availability according to the route of administration;
- concentration of the veterinary antimicrobial drug at the site of infection and its distribution in the treated animal;
- metabolism which may lead to the inactivation of veterinary antimicrobial drugs;
- excretion routes.

21. The use of fixed combinations of veterinary antimicrobial drugs should be justified taking into account:

- pharmacodynamic (additive or synergistic effects towards the target microorganism);
- pharmacokinetics (maintenance of the concentrations of associated antimicrobials responsible for additive or synergistic effects at the site of infection throughout the treatment period).

22. Clinical data should be generated to confirm the validity of the claimed indications and dosage regimens established during the preclinical phase.

23. Criteria to be considered include:

- parameters for qualitatively and quantitatively assessing efficacy;
- diversity of the clinical cases met when carrying out clinical trials;
- compliance of the protocols of clinical trials with good clinical practice, such as VICH guidelines³;
- eligibility of the studied clinical cases based on appropriate clinical and microbiological criteria.

ASSESSMENT OF THE POTENTIAL OF VETERINARY ANTIMICROBIAL DRUGS TO SELECT FOR RESISTANT MICROORGANISMS

24. Where applicable, data from preclinical or clinical trials should be used to evaluate the potential for target microorganisms, foodborne and/or commensal microorganisms to develop or acquire resistance.

25. Appropriate information should be provided to support an adequate assessment of the safety of veterinary antimicrobial drugs being considered for authorisation in food-producing animals. The regulatory authorities should develop criteria for conducting such assessments and interpreting their results. Existing guidelines for antimicrobial resistance risk assessment, such as the OIE Guideline⁴ may be used for more comprehensive information. The type of information to be evaluated in these assessments may include, but is not limited to, the following:

- the route and level of human exposure to food-borne or other resistant microorganisms;
- the degree of cross resistance within the class of antimicrobials and between classes of antimicrobials;
- the pre-existing level of resistance, if available, in pathogens causing gastrointestinal infections in humans (baseline determination);
- the concentration of active compound in the gut of the animal at the defined dosage level.

ESTABLISHMENT OF ADIs (ACCEPTABLE DAILY INTAKE), MRLs (MAXIMUM RESIDUE LIMIT), AND WITHDRAWAL PERIODS FOR VETERINARY ANTIMICROBIAL DRUGS

26. When setting ADIs and MRLs for veterinary antimicrobial drugs, the safety evaluation is carried out in accordance with international guidelines and should include the determination of microbiological effects (e.g., the potential biological effects on the human intestinal flora) as well as toxicological and pharmacological effects.

³ VICH Good Clinical Practice Guideline, http://vich.eudra.org/pdf/2000/GI09_st7.pdf

⁴ Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin, http://www.oie.int/eng/publicat/rt/2003a_r20314.htm

27. An acceptable daily intake (ADI) and a maximum residue limit (MRL) for appropriate food stuffs (i.e., meat, milk, eggs, fish and honey) should be established for each antimicrobial agent. MRLs are necessary in order that officially recognised control laboratories can monitor that the veterinary antimicrobial drugs are being used as approved. Withdrawal periods should be established for each veterinary antimicrobial drug, which make it possible to produce food in compliance with the MRLs.

28. Withdrawal periods have to be established for each veterinary antimicrobial drug by taking into account:

- the MRLs established for the considered veterinary antimicrobial drug;
- the pharmaceutical form;
- the target animal species;
- the dosage regimen and the duration of treatment;
- the route of administration.

ESTABLISHMENT OF A SUMMARY OF PRODUCT CHARACTERISTICS FOR EACH VETERINARY ANTIMICROBIAL DRUG FOR FOOD-PRODUCING ANIMALS

29. The summary of product characteristics contains the information necessary for the appropriate use of veterinary antimicrobial drugs. It constitutes, for each veterinary antimicrobial drug, the official reference of the content of its labelling and package insert. This summary contains the following items:

- pharmacological properties;
- target animal species;
- indications;
- target microorganisms;
- dosage and administration route;
- withdrawal periods;
- incompatibilities;
- shelf-life;
- operator safety;
- particular precautions before use;
- instructions for the return or proper disposal of un-used or out-of-date products;
- any information on conditions of use relevant to the potential for selection of resistance should be included, for the purpose of guidance on prudent use;
- class and active ingredient of the veterinary antimicrobial drug.

SURVEILLANCE PROGRAMMES

30. The relevant authorities should develop a structured approach to the investigation and reporting of the incidence and prevalence of antimicrobial resistance. For the purposes of this Code, priority should be given to the evaluation of antimicrobial resistance in foodborne microorganisms.

For reasons of efficiency, the methods used to establish such programmes (laboratory techniques, sampling, choice of veterinary antimicrobial drug(s) and microorganism(s)) should be harmonized as much as possible at the international level (e.g. OIE documents on “Harmonisation of National Antimicrobial Resistance Monitoring and Surveillance Programmes in Animals and Animal Derived Food” http://www.oie.int/eng/publicat/rt/2003/a_r20318.htm and “Standardisation and Harmonisation of Laboratory Methodologies Used for the Detection and Quantification of Antimicrobial Resistance” http://www.oie.int/eng/publicat/rt/2003/a_r20317.htm).

31. Preferably, epidemiological surveillance of antimicrobial resistance should be accompanied by data on the amounts of veterinary antimicrobial drugs used by veterinarians and other authorized users in food-producing animals. These data could be collected using one or more of the following sources:

- production data from manufacturers;
- importers and exporters;
- if possible, data on intended and actual usage from manufacturers, wholesale and retail distributors including feed mills, and veterinary prescription records;
- surveys of veterinarians, farmers and producers of food-producing animals.

32. Regulatory authorities should have in place a pharmacovigilance programme for the monitoring and reporting of adverse reactions to veterinary antimicrobial drugs, including lack of the expected efficacy related to microbial resistance. The information collected through the pharmacovigilance programme should form part of the comprehensive strategy to minimize microbial resistance.

33. In cases, where the assessment of data collected from pharmacovigilance and from other post-authorization surveillance including, if available, targeted surveillance of antimicrobial resistance, suggests that the conditions of use of the given veterinary antimicrobial drug should be reviewed, regulatory authorities shall endeavour to achieve this re-evaluation.

DISTRIBUTION OF VETERINARY ANTIMICROBIAL DRUGS IN VETERINARY MEDICINE

34. The relevant authorities should make sure that all veterinary antimicrobial drugs used in food-producing animals are, to the extent possible:

- prescribed by a veterinarian or other suitably trained person authorized in accordance with national legislation or used under conditions stipulated in the national legislation;
- supplied only through licensed/authorized distribution systems;
- administered to animals by a veterinarian or, under the supervision of a veterinarian or other suitably trained person authorized in accordance with national legislation; and that
- proper records are kept of their administration (see Paragraph 58, Responsibilities of Veterinarians: Recording section).

CONTROL OF ADVERTISING

35. Advertising of veterinary antimicrobial drugs should be done in a manner consistent with prudent use guidelines and any other specific regulatory recommendation for the product.

All advertising of veterinary antimicrobial drugs should be controlled by the relevant authorities.

- The authorities should ensure that advertising of veterinary antimicrobial drugs:
 - complies with the marketing authorisation granted, in particular with the content of the summary of product characteristics; and
 - complies with each country’s national legislation.

TRAINING OF USERS OF VETERINARY ANTIMICROBIAL DRUGS

36. Training should be undertaken to assure the safety to the consumer of animal derived food and therefore the protection of public health. Training should involve all the relevant professional organisations, regulatory authorities, the pharmaceutical industry, veterinary schools, research institutes, professional associations and other approved users such as farmers and producers of food animals and should focus on:

- information on disease prevention and management strategies to reduce the need to use veterinary antimicrobial drugs;
- relevant pharmacokinetic and pharmacodynamic information to enable the veterinarian to use veterinary antimicrobial drugs prudently;
- the ability of veterinary antimicrobial drugs to select for resistant microorganisms in food-producing animals that may contribute to animal or human health problems; and
- the need to observe responsible use recommendations and using veterinary antimicrobial drugs in animal husbandry in agreement with the provisions of the marketing authorisations and veterinary advice.

DEVELOPMENT OF RESEARCH

37. The relevant authorities should encourage public and private research to:

- improve the knowledge about the mechanisms of action of antimicrobials in order to optimise the dosage regimens and their efficacy;
- improve the knowledge about the mechanisms of selection, emergence and dissemination of resistance determinants;
- develop practical models for applying the concept of risk analysis to assess the public health concern precipitated by the development of resistance;
- further develop protocols to predict, during the authorisation process, the impact of the proposed use of the veterinary antimicrobial drugs on the rate and extent of resistance development; and
- develop and encourage alternative methods to prevent infectious diseases.

COLLECTION AND DESTRUCTION OF UNUSED VETERINARY ANTIMICROBIAL DRUGS

38. The relevant authorities should develop effective procedures for the safe collection and destruction of unused or out-of-date veterinary antimicrobial drugs.

RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY

MARKETING AUTHORISATION OF VETERINARY ANTIMICROBIAL DRUGS FOR FOOD-PRODUCING ANIMALS

39. It is the responsibility of the veterinary pharmaceutical industry:

- to supply all of the information requested by the national regulatory authority in order to establish objectively the quality, safety and efficacy of veterinary antimicrobial drugs; and
- to ensure the quality of this information on the basis of the implementation of procedures, tests and trials in compliance with the provisions of good manufacturing, good laboratory and good clinical practices.

MARKETING AND EXPORT OF VETERINARY ANTIMICROBIAL DRUGS

40. Only officially licensed/authorized veterinary antimicrobial drugs should be marketed, and then only through approved distribution systems.

- Only veterinary antimicrobial drugs meeting the quality standards of the importing country should be exported from a country in which the products were produced;
- The information necessary to evaluate the amount of veterinary antimicrobial drugs marketed should be provided to the national regulatory authority.

ADVERTISING

41. It is the responsibility of the veterinary pharmaceutical industry to advertise veterinary antimicrobial drugs in accordance with the provisions of Paragraph 35 on the Responsibilities of the Regulatory Authorities, Control of Advertising and to not inappropriately advertise antimicrobials directly to the food animal producer.

TRAINING

42. It is the responsibility of the veterinary pharmaceutical industry to participate in the training of users of veterinary antimicrobial drugs as defined in Paragraph 36.

RESEARCH

43. It is the responsibility of the veterinary pharmaceutical industry to contribute to the development of research as defined in Paragraph 37.

RESPONSIBILITIES OF WHOLESALE AND RETAIL DISTRIBUTORS

44. Retailers distributing veterinary antimicrobial drugs should only do so on the prescription of a veterinarian or other suitably trained person authorized in accordance with national legislation and all products should be appropriately labelled.

45. Distributors should encourage compliance with the national guidelines on the responsible use of veterinary antimicrobial drugs and should keep detailed records of all antimicrobials supplied according to the national regulations including:

- date of supply
- name of prescribing veterinarian
- name of user
- name of medicinal product
- batch number
- quantity supplied

46. Distributors should participate in the training of users of veterinary antimicrobial drugs as defined in Paragraph 36.

RESPONSIBILITIES OF VETERINARIANS⁵

47. The veterinarian is responsible for identifying recurrent disease problems and developing alternative strategies to prevent or treat infectious disease. These may include changes in husbandry conditions and vaccination programs where vaccines are available.

⁵ Under some circumstances, this may refer to a suitably trained person authorized in accordance with national legislation.

48. Veterinary antimicrobial drugs should only be prescribed for animals under his/her care, which means that:

- the veterinarian has been given responsibility for the health of the animal or herd/flock by the producer or the producer's agent;
- that responsibility is real and not merely nominal;
- that the animal(s) or herd/flock have been seen immediately before the prescription and supply, or
- recently enough for the veterinarian to have personal knowledge of the condition of the animal(s) or current health status of the herd or flock to make a diagnosis and prescribe; and
- the veterinarian should maintain clinical records of the animal(s) or the herd/flock.

49. It is recommended that veterinary professional organizations develop for their members species-specific clinical practice guidelines on the responsible use of veterinary antimicrobial drugs.

50. Veterinary antimicrobial drugs should only be used when necessary and in an appropriate manner:

- A prescription for veterinary antimicrobial drugs must precisely indicate the treatment regimen, the dose, the dosage intervals, the duration of the treatment, the withdrawal period and the amount of antimicrobial to be delivered depending on the dosage, the number, and the weight of the animals to be treated;
- All veterinary antimicrobial drugs should be prescribed and used according to the conditions stipulated in the national legislation.

51. The appropriate use of veterinary antimicrobial drugs in practice is a clinical decision which should be based on the experience and local expertise of the prescribing veterinarian, and the accurate diagnosis, based on adequate diagnostic procedures. There will be occasions when a group of animals, which may have been exposed to pathogens, may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing in order to prevent the development of clinical disease and for reasons of animal welfare.

52. Determination of the choice of a veterinary antimicrobial drug by:

- The expected efficacy of the treatment based on:
 - the clinical experience of the veterinarian;
 - the spectrum of the antimicrobial activity towards the pathogens involved;
 - the epidemiological history of the rearing unit particularly in regards to the antimicrobial resistance profiles of the pathogens involved. Ideally, the antimicrobial profiles should be established before the commencement of treatment. Should a first antimicrobial treatment fail or should the disease recur, the use of a second veterinary antimicrobial drug should be based on the results of microbiological tests;
 - the appropriate route of administration;
 - results of initial treatment;
 - known pharmacokinetics/tissue distribution to ensure that the selected veterinary antimicrobial drug is active at the site of infection;
 - prognosis.
- The need to minimize the adverse health impact from the development of microbial resistance based on:
 - the choice of the activity spectrum of the veterinary antimicrobial drug;

- the targeting of specific microorganism;
- known or predictable susceptibilities using antimicrobial susceptibility testing;
- optimized dosing regimens;
- the use of effective combinations of veterinary antimicrobial drugs;
- the importance of the antimicrobial drugs to veterinary and human medicine; and,
- the route of administration.

53. If the label conditions allow for some flexibility, the veterinarian should consider a dosage regimen that is long enough to allow an effective recovery of the animal but is short enough to limit the selection of resistance in foodborne and/or commensal microorganisms.

OFF-LABEL USE

54. The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the administrative withdrawal periods to be used. It is the veterinarian's responsibility to define the conditions of responsible use in such a case including the therapeutic regimen, the route of administration, and the duration of the treatment. Off-label use of antimicrobial growth promoters should not be permitted.

RECORDING

55. Records on veterinary antimicrobial drugs should be kept in conformity with national legislation. Veterinarians may refer to recording information as covered in the relevant national legislation.⁶

In particular, for investigation of antimicrobial resistance, veterinarians should:

- record the antimicrobial susceptibility testing results;
- investigate adverse reactions to veterinary antimicrobial drugs, including lack of expected efficacy due to antimicrobial resistance, and report it, as appropriate, to the regulatory authorities.

56. Veterinarians should also periodically review farm records on the use of veterinary antimicrobial drugs to ensure compliance with their directions.

TRAINING

57. Veterinary professional organizations should participate in the training of users of veterinary antimicrobial drugs as defined in Paragraph 36.

RESPONSIBILITIES OF PRODUCERS

58. Producers are responsible for preventing disease outbreaks and implementing health and welfare programmes on their farms. They may, as appropriate, call on the assistance of their veterinarian or other suitably trained person authorized in accordance with national legislation. All people involved with food-producing animals have an important part to play in ensuring the responsible use of veterinary antimicrobial drugs.

59. Producers of food-producing animals have the following responsibilities:

- to use veterinary antimicrobial drugs only when necessary and not as a replacement for good management and farm hygiene, or other disease prevention methods such as vaccination;

⁶ Veterinarians can also refer to the "Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993."

- to implement a health plan in cooperation with the veterinarian in charge of the animals that outlines preventative measures (e.g. mastitis plan, worming and vaccination programmes, etc.);
- to use veterinary antimicrobial drugs in the species, for the uses and at the doses on the approved labels and in accordance with the prescription, product label instructions or the advice of a veterinarian familiar with the animals and the production site;
- to isolate sick animals and dispose of dead or dying animals promptly under conditions approved by relevant authorities;
- to comply with the storage conditions of veterinary antimicrobial drugs according to the approved product labelling;
- to address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated;
- to comply with the recommended withdrawal periods to ensure that residue levels in animal derived food do not present a risk for the consumer;
- to not use out-of-date veterinary antimicrobial drugs and to dispose of all unused veterinary antimicrobial drugs in accordance with the provisions on the product labels;
- to inform the veterinarian in charge of the unit of recurrent disease problems;
- to maintain all clinical and laboratory records of microbiological and susceptibility tests if required by the national regulatory authority. These data should be made available to the veterinarian in charge of treating the animals in order to optimize the use of veterinary antimicrobial drugs.
- To keep adequate records of all veterinary antimicrobial drugs used, including the following:
 - name of the veterinary antimicrobial drug/active substance and batch number;
 - name of supplier;
 - date of administration;
 - identification of the animal or group of animals to which the veterinary antimicrobial drug was administered;
 - clinical conditions treated;
 - quantity and duration of the antimicrobial agent administered;
 - withdrawal periods;
 - result of laboratory tests;
 - result of treatment;
 - name of the prescribing veterinarian or other suitably trained person authorized in accordance with national legislation.
- To ensure sound management of animal wastes and other materials to avoid dissemination of antimicrobial agents and resistance determinants into the environment;
- To prevent the unnecessary contact with and transmission of resistant bacteria to all personnel, including farm workers;
- To assist the relevant authorities in surveillance programs related to antimicrobial resistance.

CONCLUSIONS

60. Veterinary antimicrobial drugs are very important tools for controlling a great number of infectious diseases in both animals and humans. It is vital that all countries put in place the appropriate systems to ensure that veterinary antimicrobial drugs are manufactured, marketed, distributed, prescribed and used responsibly, and that these systems are adequately audited.

61. This document is designed to provide the framework that countries may implement in accordance with their capabilities but within a reasonable period of time. A stepwise approach may be appropriate for a number of countries to properly implement all of the elements in this document.

62. The continued availability of veterinary antimicrobial drugs, which are essential for animal welfare and animal health and consequently human health, will ultimately depend on the responsible use of these products by all those involved in the authorisation, production, control, distribution and use of antimicrobials in food-producing animals.

ENDNOTES:

¹A. Franklin, J. Acar, F. Anthony, R. Gupta †T. Nicholls, Y. Tamura, S. Thompson, E.J. Threlfall, D. Vose, M. van Vuuren, D.G. White, H. C. Wegener & M.L. Costarrica. *Antimicrobial resistance: harmonization of national antimicrobial resistance monitoring and surveillance programmes in animals and in animal-derived food*. *Rev. sci. tech. Off. Int. Epiz.*, **20** (3), 859-870. http://www.oie.int/eng/publicat/rt/2003/a_r20318.htm

²D.G. White, J. Acar, F. Anthony, A. Franklin, R. Gupta, †T. Nicholls, Y. Tamura, S. Thompson, E.J. Threlfall, D. Vose, M. van Vuuren, H. C. Wegener & M.L. Costarrica. *Antimicrobial resistance: standardization and harmonization of laboratory methodologies for the detection and quantification of antimicrobial resistance*. *Rev. sci. tech. Off. Int. Epiz.*, 2001, **20** (3), 849-858. http://www.oie.int/eng/publicat/rt/2003/a_r20317.htm

LIST OF ABBREVIATIONS USED IN THIS CODE

| | |
|---------|--|
| ADI | Acceptable Daily Intake |
| CAC | Codex Alimentarius Commission |
| CAC/RCP | Codex Alimentarius Commission/Recommended Code of Practice |
| CCRVDF | Codex Committee on Residues of Veterinary Drugs in Foods |
| FAO | Food and Agriculture Organization of the United Nations |
| MRL | Maximum Residue Limit |
| OIE | Office International des epizooties/International Office of Epizooties |
| VICH | International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products |
| WHO | World Health Organization |

GLOSSARY AND DEFINITIONS OF TERMS

Veterinary Antimicrobial Drug

Veterinary antimicrobial drug(s) refers to naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of microorganisms). Where anticoccidial products have antibacterial activity, they should be considered as veterinary antimicrobial drugs, except where this is precluded by national legislation.

Disease Treatment/Therapeutic Use

Treatment/Therapeutic Use refers to use of an antimicrobial(s) for the specific purpose of treating an animal(s) with a clinically diagnosed infectious disease or illness.

Disease Prevention/Prophylactic Use

Prevention/Prophylactic Use refers to use of an antimicrobial(s) in healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. This treatment includes:

- control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and
- prevention of an infectious disease that has not yet been clinically diagnosed.

Growth Promotion

Growth Promotion refers to the use of antimicrobial substances to increase the rate of weight gain and/or the efficiency of feed utilization in animals by other than purely nutritional means. The term does NOT apply to the use of antimicrobials for the specific purpose of treating, controlling, or preventing infectious diseases, even when an incidental growth response may be obtained.