codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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CX 4/60.2 **CL 2003/40-RVDF**
November 2003

TO: Codex Contact Points
Interested International Organizations

FROM: Secretary, Joint FAO/WHO Food Standards Programme
c/o FAO, 00100 Rome, Italy

SUBJECT: **Request for Comments on the Revised Proposed Draft Code of Practice to Minimize and Contain Antimicrobial Resistance**

DEADLINE: **30 April 2004**

COMMENTS:

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BACKGROUND

The 14th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (4-7 March 2003) had general discussions on document CX/RVDF 03/6 "Proposed Draft Code of Practice to Minimize and Contain Antimicrobial Resistance". The Committee decided to request additional comments on the proposed draft Code and agreed that a drafting group, under the direction of the United States, with participants from Australia, Brazil, Canada, Costa Rica, Denmark, Finland, France, Ireland, Germany, New Zealand, Sweden, Thailand, United Kingdom, OIE, WHO, European Community, International Federation for Animal Health, and Consumers International, would prepare a revised version of the proposed draft Code of Practice for circulation, comments and further consideration at its 15th Session (25-28 October 2004). The Committee agreed that the proposed draft Code of Practice would be revised by the drafting group on the basis of the discussion, written comments submitted at its 14th Session and comments submitted in response to CL 2003/11-RVDF, Part B (ii) (ALINORM 03/31A, paras. 79-80).

Several members of the drafting group met in Rockville, Maryland July 14-15 to address the CCRVDF directions on finalizing the draft Code of Practice. The meeting was very successful and accomplished the following:

- Redrafted the Code of Practice based on written comments received by Codex and comments received at the 14th session of the CCRVDF
- Developed a Glossary of Terms and Definitions that includes definitions for Antimicrobial, Treatment/Therapeutic Use, Prevention/Prophylactic Use, and Growth Promotion
- Addressed the environmental concerns by incorporating the issue points in the old Paragraphs 26 and 57 into a new fourth paragraph in the Introduction section and an additional paragraph (seventh) in the Aims and Objectives section. The latter paragraph specifically references the VICH Environmental Impact Assessment for Veterinary Medicinal Products, Phase I.

The revised document was sent to the entire drafting group for further comments which were incorporated in the attached revised proposed draft Code.

REQUEST FOR COMMENTS

Governments and international organizations are invited to comment at Step 3, as directed above, on the Revised Proposed Draft Code of Practice to Minimize and Contain Antimicrobial Resistance, annexed to this Circular Letter, in conformity with the Procedures for the Elaboration of Codex Standards and Related Texts (see *Codex Alimentarius Procedural Manual*, Thirteenth Edition, pages. 19-22) **not later than 30 April 2004**.

Annex

REVISED PROPOSED DRAFT CODE OF PRACTICE TO MINIMIZE AND CONTAIN ANTIMICROBIAL RESISTANCE

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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 antimicrobials 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, pharmacists and producers of food-producing animals.

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

3. A number of codes of practice relating to the use of antimicrobials 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 and to protect the health of consumers.

6. Antimicrobial agents are powerful tools for the management of infectious diseases in animals and humans. This Code and existing guidelines for the responsible use of antimicrobial agents 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 keep animals in good health.

7. Codex does not specifically cover environmental issues; however, antimicrobial resistant microorganisms do not recognize such jurisdictional boundaries. This Code does not address environmental issues related to antimicrobial resistance from the use of veterinary medicinal products 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 antimicrobial agents, antimicrobial resistant organisms and resistance determinants are kept to a minimum. In particular:

- Regulatory authorities should assess the impact of proposed antimicrobial use on the environment in accordance with national guidelines or recognized international guidelines[1]

[1] http://vich.eudra.org/pdf/2000/Gl06_st7.pdf

- Research should be conducted on resistant microorganisms in the environment and the magnitude of resistance determinant transfer among microorganims in the environment.

8. The responsible use of antimicrobials in food-producing animals:

- is controlled by the veterinary profession or other professionals 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 antimicrobial agents 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 antimicrobials 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-based evaluation. This evaluation 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 professionals, such as:

  - administrative and scientific authorities

  - the veterinary pharmaceutical industry

  - distributors and others handling antimicrobials

  - veterinarians, pharmacists and producers of food-producing animals

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 in support of prudent use of antimicrobials in food-producing animals. It is the responsibility of regulatory authorities to develop up-to-date guidelines on data requirements for evaluation of antimicrobial drug applications. National governments 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 antimicrobials 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-based evaluations, as described in Paragraph 8.

10. It is the responsibility of the pharmaceutical company or sponsor[2] 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 only if the criteria of safety, quality and efficacy are met.

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[2] As defined in the VICH Good Clinical Practice Guideline, http://vich.eudra.org/pdf/2000/Gl09_st7.pdf

- The examination of dossiers/drug applications must 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 antimicrobial product and not be generalized to 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 antimicrobials.

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. (See OIE Guidance on Antimicrobial Resistance: Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine http://www.oie.int/eng/publicat/rt/2003/Anthony.pdf.)

14. No antimicrobial 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 antimicrobial-containing formulations considered to have the potential to make an important contribution in the control of antimicrobial resistance. Restrictions in off-label use should be considered for antimicrobials that are of critical importance for human medicine. The elaboration of internationally accepted guidelines would assist in this regard.

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

- ensure the efficacy of their administrative controls on the import of these veterinary medicinal products,
- seek information on authorizations valid in other countries, and
- develop the necessary technical cooperation with experienced authorities to check the quality of imported veterinary medicinal products 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 medicinal products.

16. All countries should make every effort to actively combat the manufacture, trade, distribution and use of illegal and counterfeit bulk active pharmaceutical ingredients and products. Regulatory authorities of importing countries could request the pharmaceutical industry to provide quality certificates 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 antimicrobial agents 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 antimicrobials when they are mixed with feed or drinking water.
- to ensure that all antimicrobials 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 antimicrobial agent and limit the selection of antimicrobial resistant microorganisms. Such preclinical trials should 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 medicinal;
- 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 antimicrobial at the site of infection and its distribution in the treated animal;
- metabolism which may lead to the inactivation of antimicrobials;
- excretion routes.

21. The use of fixed combinations of antimicrobial agents 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 guidelines[3];
- eligibility of the studied clinical cases based on appropriate clinical and microbiological criteria.

Assessment of the potential of antimicrobials 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 antimicrobial products 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 Guideline[4] 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:

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[3] VICH Good Clinical Practice Guideline , http://vich.eudra.org/pdf/2000/Gl09_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

- the level of human exposure to foodborne 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 antimicrobial compounds

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

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

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

- the MRLs established for the considered antimicrobial agent;
- 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 antimicrobial for food-producing animals

29. The summary of product characteristics contains the information necessary for the appropriate use of veterinary medicinal products containing antimicrobial agents. It constitutes, for each veterinary medicinal product, 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.

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 antimicrobial agent(s) and microorganism(s)) should be harmonized as much as possible at the international level (see 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 antimicrobial agents 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, distributors including feed mills, pharmacies 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 medicinal products, including lack of the expected efficacy related to antimicrobial resistance. The information collected through the pharmacovigilance programme should form part of the comprehensive strategy to minimize antimicrobial resistance.

33. If justified by the results of this post authorization surveillance of antimicrobial resistance, the conditions of use of the antimicrobial agent in veterinary medicine should be re-evaluated. This re-evaluation may include data obtained from targeted surveillance.

Distribution of the antimicrobial agents in veterinary medicine

34. The relevant authorities should make sure that all the antimicrobial agents 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;
- delivered by an authorized animal health professional;
- 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 antimicrobials should be done in a manner consistent with prudent use guidelines and any other specific regulatory recommendation for the product.

All advertising of antimicrobials should be controlled by the relevant authorities.

- The authorities should ensure that advertising of antimicrobial products:
    - 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 antimicrobial users

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, including regulatory authorities, the pharmaceutical industry, veterinary schools, research institutes and professional associations and should focus on:

- information on disease prevention and management strategies to reduce the need to use antimicrobials;
- relevant pharmacokinetic and pharmacodynamic information to enable the veterinarian to use antimicrobials prudently;
- the ability of antimicrobials 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 antimicrobial agents 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 resistant microorganisms;
- further develop protocols to predict, during the authorisation process, the impact of the proposed use of the antimicrobials on the rate and extent of resistance development; and
- develop and encourage alternative methods to prevent infectious diseases.

Collection and destruction of unused products and containers

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

RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY

Marketing authorisation of antimicrobials 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 medicinal products; 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.

40. The veterinary pharmaceutical industry should be encouraged to carry out post-approval studies, as is done for human medicinal products, in order to seek an extension of the authorised indications in light of practical experience. This would in effect limit the need for off-label use. Post approval studies could also serve to revalidate the safety and efficacy of the products.

Marketing and export of veterinary medicinal products

41. Only officially licensed/authorized veterinary medicinal products should be marketed, and then only through approved distribution systems.

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

Advertising

42. It is the responsibility of the veterinary pharmaceutical industry to advertise veterinary medical products 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

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

Research

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

RESPONSIBILITIES OF PHARMACISTS AND/OR DISTRIBUTORS

45. Pharmacists distributing veterinary antimicrobials should only do so on the prescription of a veterinarian or other appropriately authorized person and all products should be appropriately labelled.

46. Pharmacists should reinforce the guidelines on the responsible use of antimicrobials. In addition, pharmacists 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

47. Pharmacists should participate in the training of antimicrobial users as defined in Paragraph 36.

RESPONSIBILITIES OF VETERINARIANS [5]

48. 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.

49. Antimicrobials 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

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

- 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.

50. It is recommended that veterinary professional organizations develop for their members species-specific clinical practice guidelines on the responsible use of antimicrobials, with particular reference to the choice of veterinary medicinal products, disease prevention strategies and treatment protocols.

51. Antimicrobial agents should only be used when necessary and in an appropriate manner:

- A prescription for antimicrobial agents 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 antimicrobial veterinary medicinal products should be prescribed and used according to the conditions of the marketing authorization, which are reflected in the approved summary of product characteristics;
- Antimicrobial agents should be used in a manner that limits their administration to diseased animals or animals requiring therapeutic treatment.

52. The appropriate use of antimicrobials 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.

53. Determination of the choice of an antimicrobial 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 antimicrobial agent 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 antimicrobial agent is active at the site of infection
    - prognosis
- The absence of selection or limited selection of antimicrobial resistant microorganisms which is influenced by:
    - the choice of the activity spectrum of the antimicrobial
    - the targeting of specific microorganism
    - known or predictable susceptibilities using antimicrobial susceptibility testing
    - optimized dosing regimens
    - the use of effective combinations of antimicrobial agents
    - the importance of the antimicrobial agents to veterinary and human medicine, and
    - the route of administration

54. Combinations of antimicrobials

- Combinations of antimicrobials are used for their synergistic effect to increase efficacy or to broaden the spectrum of activity;
- If the use of a combination of antimicrobials is justified, the veterinarian should make sure that there is no antagonism between the chosen antimicrobials, and
- The veterinarian should check the ability of these antimicrobials to reach the infection site under similar time and concentration conditions, to maintain effective therapeutic concentrations as long as is needed;
- A bad choice of a combination of antimicrobials may in certain cases lead to an increase of selection of resistance;
- On the other hand, the use of combinations of antimicrobials can be protective against the selection of resistance in cases where microorganisms exhibit a high mutation rate against a given antimicrobial.

55. 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 of antimicrobial veterinary medicinal products

56. Although all antimicrobial veterinary medicinal products should be prescribed and used in accordance with the specifications of the marketing authorization, the prescribing veterinarian should have the discretion to adapt these in exceptional circumstances.

57. The off-label use of an antimicrobial agent 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

58. Records on veterinary medicinal products should be kept in conformity with national legislation. Veterinarians may refer to recording information as covered in "Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993."

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

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

59. Veterinarians should also periodically review farm records on antimicrobial use.

Training

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

RESPONSIBILITIES OF PRODUCERS

61. 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 antimicrobials.

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

- to use antimicrobial products only when necessary and not as a replacement for good management and farm hygiene, or other disease prevention methods such as vaccination;
- to draw up a health plan with the veterinarian in charge of the animals that outlines preventative measures (e.g. mastitis plan, worming and vaccination programmes, etc.);
- to use antimicrobial agents 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;
- to comply with the storage conditions of antimicrobials 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 medicines and to dispose of all unused medicines 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 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 antimicrobials.
- To keep adequate records of all veterinary medicinal products used, including the following:
    - name of the veterinary medicinal product/active substance and batch number
    - name of supplier
    - date of administration
    - identification of the animal or group of animals to which the antimicrobial agent was administered
    - clinical conditions treated
    - quantity 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.

CONCLUSIONS

63. Antimicrobial agents 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 antimicrobials are manufactured, marketed, distributed, prescribed and used responsibly, and that these systems are adequately audited.

64. 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.

65. The continued availability of antimicrobial veterinary medicinal products, 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:

[1]A. 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

[2]D.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 REPORT

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

Antimicrobial

Antimicrobial agents or antimicrobial(s) refer to naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of microorganisms.)

The term Antimicrobial(s) includes:

- antibiotics, which refer to substances produced by or derived from microorganisms, and
- anticoccidials, which refer to substances that are active against coccidia, single cell protozoan parasites.

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.