codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00100 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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PROPOSED DRAFT CODE OF PRACTICE TO MINIMIZE AND CONTAIN ANTIMICROBIAL RESISTANCE

Governments and international organizations wishing to submit comments on the following subject matter are invited to do so **no later than 3 February 2003** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th and Independence Avenue, S.W., Washington, DC 20250, USA (Fax No: +1.202.720.3157; e-mail: uscodex@usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org).

Background

The 13th Session (December 2001) of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) considered a discussion paper on Antimicrobial Resistance and the Use of Antimicrobials in Animal Production and confirmed the decision taken during its 12th Session that the CCRVDF should develop a code of practice for the containment of antimicrobial resistance. The Committee therefore agreed that the delegation of the United States, with the assistance of Australia, Brazil, Canada, China, Costa Rica, Denmark, Finland, France, Germany, New Zealand, Sweden, Thailand, United Kingdom, CI, EC, FAO, IFAH, OIE and WHO, would further elaborate a proposed draft Code of Practice to Minimize and Contain Antimicrobial Resistance for circulation, comment and further consideration at its next Session (ALINORM 03/31, paras 71-77). The 50th Executive Committee approved the CCRVDF proposal to initiate new work on the elaboration on the draft Code (ALINORM 03/3A, para. 64 and Appendix III).

Introduction

The U.S. chaired the Codex Committee on Residues of Veterinary Drugs in Foods working group to draft a Code of Containment to Minimize and Contain Antimicrobial Resistance in food-producing animals. During the course of drafting the Code, the working group had identified several issues that require further guidance from the CCRVDF before including in the document. Specifically, the working group had identified several topics that, although relevant to the issue of antimicrobial resistance, may be outside of the terms of reference of the CCRVDF.

The U.S. indicated that the working group would like explore the feasibility of the CCRVDF rendering an opinion to the working group as to which of these topics, if any, should be the subject of further elaboration by the working group and ultimately, incorporation into the Code.

ISSUES FOR CONSIDERATION
- Definitions for "non-therapeutic" and “therapeutic”
- Establishing the criteria and/or definition of a "critical human disease(s) and drugs of importance to human medical therapy
- Environmental concerns
- Determination of the concentration of active compound in the gut of the animal at the defined dosage level

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 antimicrobial in veterinary medicine by maintaining their efficacy. It defines the respective responsibilities of authorities and groups involved in the authorisation, production, control, distribution and use of veterinary antimicrobials such as national competent authorities, the veterinary pharmaceutical industry, veterinarians, pharmacists, and producers of food-producing animals.

2. The basis for prudent use of antimicrobials in food-producing animals is mainly determined by the outcome of the marketing authorisation procedure. This includes the implementation of the labelled indications for use and any warning statements that are present.

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.

AIMS AND OBJECTIVES

4. 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 bacteria among animals and to protect the health of consumers.

5. Antimicrobial agents are powerful tools for treating and preventing/controlling bacterial diseases in animals. Guidelines for the responsible use of antimicrobial agents in food-producing animals include recommendations intended to prevent or reduce the selection of antimicrobial resistant bacteria in animals 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 transfer of resistant bacteria or resistance determinants within animal populations and from animals to man.
- 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

6. 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 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 therapy when problems become evident
- should be based on the results of resistance surveillance and monitoring (bacterial cultures and antimicrobial sensitivity testing), as well as clinical experience.

- does not include the non-therapeutic[1] use 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 by the appropriate national authorities of the potential to impact antimicrobial resistance in the human population.
- 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 livestock producers

RESPONSIBILITIES OF THE REGULATORY AUTHORITIES

7. 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 the 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 antimicrobial 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, vaccination policies, and development of health care at the farm level, which will reduce the prevalence of animal disease requiring antimicrobial therapy. Non-therapeutic use of antimicrobials (e.g., 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.

8. It is the responsibility of the pharmaceutical industry to submit the data requested for the granting of the marketing authorisation.

9. The use of an antimicrobial agent in food-producing animals requires a marketing authorisation, granted by the competent authorities only if the criteria of safety, quality and efficacy are met.

- the examination of dossiers/drug applications must include an assessment of the risks to both the animal and the consumer 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 food animals associated with the use of antimicrobials.

10. If dose ranges or different duration of treatment are suggested, 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. The relevant authorities should, where possible, make sure that all the antimicrobial agents used in food animals are prescribed by a veterinarian or other suitably trained and authorized persons. In cases where it is not possible to administer these products on a prescription-only basis, individuals should refer to the internationally recognized guidance on prudent use for guidance on proper

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1 The drafting group acknowledges that a glossary definition needs to be provided for this term. The drafting group is awaiting direction from the CCRVDF as to whether this group or another group should elaborate on these definitions.

2 The drafting group acknowledges that a glossary definition needs to be provided for this term. The drafting group is awaiting direction from the CCRVDF as to whether this group or another group should elaborate on these definitions.

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

11. 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. Limitation of off label use should be considered for antimicrobials that are important to human medicine[3]. 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 resistance. The elaboration of internationally accepted guidelines would assist in this regard.

12. 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
- ensure the validity of the authorisation procedures of the exporting country
- 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.

13. Regulatory authorities of importing countries could request the pharmaceutical industry to provide quality certificates prepared by the exporting country's competent authority. 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.

Quality control of antimicrobial agents

14. 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 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 the therapeutic[4] efficacy

15. Preclinical data should be generated to:

- establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit the selection of antimicrobial resistant bacteria. Such preclinical trials may include pharmacokinetic and pharmacodynamic studies to guide the development of the most appropriate dosage regimen.

16. Important pharmacodynamic information may include:

- mode of action
- minimum inhibitory and bactericidal concentrations
- time or concentration-dependent activity

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[3] The drafting group acknowledges that a glossary definition needs to be provided for the phrase "antimicrobials that are important to human medicine". The drafting group is awaiting direction from the CCRVDF as to whether this group or another group should elaborate on this phrase.

[4] The drafting group acknowledges that a glossary definition needs to be provided for this term. The drafting group is awaiting direction from the CCRVDF as to whether this group or another group should elaborate on these definitions.

- activity at the site of infection

17. 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

18. The use of fixed combinations of antimicrobial agents should be justified taking into account:

- pharmacodynamics (additive or synergistic effects towards the target bacteria)
- pharmacokinetics (maintenance of the levels of associated antimicrobials responsible for additive or synergistic effects at the site of infection throughout the treatment period)

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

20. Criteria to be considered:

- diversity of the clinical cases met when carrying out clinical trials
- compliance of the protocols of clinical trials with good clinical practice
- eligibility of the studied clinical cases based on appropriate criteria of clinical and bacteriological diagnoses
- parameters for qualitatively and quantitatively assessing the efficacy of the treatment

Assessment of the potential of antimicrobials to select for resistant bacteria

- where applicable, data from preclinical or clinical trials should be used to evaluate not only the potential for bacteria of target animals to select for resistance, but also for the potential impact of the antimicrobial use on food borne and/or commensal bacteria
- the sponsor applying for market authorisation for antimicrobials for veterinary use should generally supply data.

21. 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. The type of information included in these assessments may include, but is not limited to, the following:

- the concentration of active compound in the gut of the animal at the defined dosage level where the majority of potential food borne pathogens reside
- the level of human exposure to food borne or other resistant bacteria
- 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 of human health concern (baseline determination)

Establishment of ADIs (acceptable daily intake), MRLs (maximum residue limit), and withdrawal periods for antimicrobial compounds

22. When setting ADIs and MRLs for antimicrobial substances, the safety evaluation should, include the determination of microbiological as well as toxicological effects (e.g., the potential biological effects on the human intestinal flora).

23. The establishment for each antimicrobial agent of an acceptable daily intake (ADI), and a maximum residue limit (MRL) for appropriate food stuffs (i.e., meat, milk, eggs and honey) , should be undertaken. MRLs are necessary in order that officially approved control laboratories can monitor that these drugs are being used according to recommended controls. 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.

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

- the MRL 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

25. The applicant should provide methods for regulatory testing of residues in food.

Protection of the environment[5]

26. An assessment of the impact of the proposed antimicrobial use on the environment should be carried out in accordance with each country's guidelines. Efforts should be made to ensure that environmental contamination with antimicrobials is kept to a minimum.

Establishment of a summary of product characteristics for each antimicrobial for food-producing animals

27. 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
- therapeutic indications
- target bacteria
- dosage and administration route
- withdrawal periods
- incompatibilities
- expiry date
- 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.

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5 The drafting group acknowledges that environmental issues may be outside of the terms of reference of the CCRVDF. The drafting group is awaiting direction from the CCRVDF as to whether this group or another group should elaborate on environmental issues.

Post-marketing antimicrobial resistance surveillance

28. There should be a structured approach to the investigation and reporting of the incidence and prevalence of resistance. Regulatory authorities should have in place a pharmacovigilance programme for the monitoring, reporting and recording of adverse reactions to antimicrobials, including the lack of efficacy related to antimicrobial resistance. The information collected through the pharmacovigilance programme should form part of the comprehensive strategy to minimise antimicrobial resistance.

Targeted surveillance

29. A surveillance programme to assess the impact of the use of antimicrobial agents, especially those intensively used, on the selection of antimicrobial resistant bacteria in food producing animals may be implemented after the granting of the marketing authorisation. In certain cases, the surveillance program should evaluate not only resistance development in target animal pathogens, but also in food borne pathogens and/or commensals.

National surveillance program

30. The surveillance of animal bacteria resistant to antimicrobial agents is recommended. The relevant authorities should implement a programme, established from the results of a risk analysis, which makes it possible to rank priorities regarding antimicrobials and animal bacteria, whether they are pathogenic or not for animals and man. For reasons of efficiency, the methods used to establish such programmes (laboratory techniques, sampling, choice of agents and bacteria) should be harmonised 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" and "Standardisation and Harmonisation of Laboratory Methodologies Used for the Detection and Quantification of Antimicrobial Resistance"([1,2]).

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 by one or more of the following sources:

- importers and exporters as well as production data from manufacturers;
- data on intended and actual usage from manufacturers, distributors including feed mills, pharmacies and veterinary prescriptions records;
- veterinarians, farmers, and animal producers

32. If justified by the results of this post authorisation surveillance of antimicrobial resistance, the conditions of use of the antimicrobial agents in veterinary medicine should be re-evaluated.

Distribution of the antimicrobial agents used in veterinary medicine

33. The relevant authorities should, where possible, make sure that all the antimicrobial agents used in food animals are:

- prescribed by a veterinarian or other suitably trained and authorized person
- 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 by his/her agent.
- Proper records kept (see Part E.4 Responsibilities of Veterinarians: Recording section)

Control of advertising

34. All advertising of antimicrobials should be controlled by the relevant authorities. The authorities should check whether the advertising of antimicrobial products:

- complies with the marketing authorisation granted, in particular with the content of the summary of product characteristics, and
- is in compliance with each country's national legislation.
- guidance should be put in place to ensure that promotion of antimicrobials is done in a manner consistent with prudent use guidelines and any other specific regulatory recommendation for the product

Training of antimicrobial users

35. This training, involving all the relevant professional organisations, including regulatory authorities, the pharmaceutical industry, veterinary schools, research institutes, and professional associations, should focus on:

- information on disease prevention and management strategies to reduce the need to prescribe antimicrobials;
- the ability of antimicrobials to select for resistant bacteria in food producing animals that may cause animal or human health problems;
- 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, in order to assure the safety to the consumer of animal derived food, and therefore the protection of public health; and
- relevant pharmacokinetic and pharmacodynamic information to enable the veterinarian to use antimicrobials prudently.

Development of research

36. The relevant authorities should encourage public and private research to

- improve the knowledge about the mechanisms of the action of antimicrobials in order to optimise the dosage regimens and the therapeutic activity of these medicinal products;
- improve the knowledge about the mechanisms of selection, emergence and dissemination of bacterial genes encoding resistance against antimicrobial agents;
- develop practical models for applying the concept of risk analysis to assess the public health concern precipitated by the development of resistant bacteria;
- 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 alternative methods to control bacterial diseases (vaccines, changes in husbandry practices, selective breeding of animals naturally resistant to pathogenic bacteria etc.).

Collection and destruction of unused products and containers

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

RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY

Marketing authorization of antimicrobials for food-producing animals

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

- to supply all the information requested by the national regulatory authority in order to establish objectively the quality, safety and efficacy of veterinary medicinal products; and
- to guarantee 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.

39. The 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 authorized indications in the 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

40. only officially licensed and approved veterinary medicinal products should be sold and supplied, and then only through licensed/authorized distribution systems

- only veterinary medicinal products meeting the quality standards of the country in which the products were produced should be exported
- to provide the national regulatory authority with the information necessary to evaluate the amount of antimicrobial agents marketed

Advertising

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

- to disseminate information in compliance with the provisions of the granted authorisation 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 programmes as defined in B. 10

Research

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

- to contribute to the research effort as defined in B.11.

RESPONSIBILITIES OF PHARMACISTS AND/OR DISTRIBUTORS

44. 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. (See Labelling under E.4.). Pharmacists should reinforce the guidelines on the responsible use of antimicrobials. In addition, pharmacists should keep detailed records of all antimicrobials supplied according to national regulations including:

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

45. Pharmacists should be involved in training programmes on the responsible use of antimicrobials.

RESPONSIBILITIES OF VETERINARIANS

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

47. Antimicrobials should only be prescribed for animals under his/her care, which means that:

- the veterinarian must have been given responsibility for the health of the animal or herd/flock by the producer or the producer's agent;
- that responsibility must be real and not merely nominal;
- that the animal(s) or herd/flock must have been seen immediately before the prescription and supply

or

- recently enough or often 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)/herd/flock

48. 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 product, disease prevention strategies and treatment protocols. The responsibilities of veterinarians in this area are the following:

Use of antimicrobial agents when necessary

The appropriate use of antimicrobials in practice is a critical decision, which, where possible, should be based on:

- the experience and local expertise of the prescribing veterinarian, and
- an accurate diagnosis, based on adequate diagnostic procedures.

There will be occasions when a group of animals, which may have been exposed to pathogenic bacteria, may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing, to prevent the development of clinical disease and for reasons of animal welfare.

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 pathogenic bacteria involved
  - the epidemiological history of the rearing unit particularly in relation to the antimicrobial resistance profiles of the pathogenic bacteria involved. Ideally, the antimicrobial profiles should be established before the commencement of treatment. Should a first line antimicrobial treatment fail or should the disease recur, the use of a second line antimicrobial agent should be based on the results of the microbiological tests.
  - the appropriate route of administration
  - results of initial treatment
  - known pharmacokinetics / tissue distribution to ensure that the selected therapeutic agent is active at the site of infection

- prognosis over what time period

In order to minimize the likelihood of antimicrobial resistance developing, it is recommended that antimicrobial be targeted to bacteria likely to be the cause of infection.

- The absence of selection or limited selection of antimicrobial resistant bacteria which is influenced by:
  - the choice of the activity spectrum of the antimicrobial
  - the targeting of specific bacteria
  - known or predictable susceptibilities using antimicrobial susceptibility testing
  - the correct dosing regimens
  - the use of effective combinations of antimicrobial agents
  - the importance of the drug to human and/ or veterinary medicine.
  - the route of administration.
- Combinations of antimicrobials
  - If the use of a combination of antibacterials is justified, the veterinarian should make sure that there is no antagonism between the chosen antibacterials and should check the ability of these antibacterials 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 antibacterials may in certain cases lead to an increase of the selection of resistance.
  - On the other hand, the use of combinations of antimicrobials can be protective against the selection of resistance in cases, where bacteria exhibit a high mutation rate against a given antimicrobial.
  - Combinations of antimicrobials are used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

Appropriate use of the antimicrobial agent chosen

- A prescription for antimicrobial agents must precisely indicate the treatment regime, the dose, the dosage intervals, the duration of the treatment, the withdrawal period and the amount of drug to be delivered depending on the dosage and the number of animals to be treated.
- All medicinal products should be prescribed and used according to the conditions of the marketing authorisation, which are reflected in the manufacturer’s summary of product characteristics.
- Antimicrobial agents should be administered in a manner that limits exposure to diseased animals or animals requiring therapeutic treatment.

49. If the label conditions allow for some flexibility the veterinarian should consider a therapeutic regimen that is long enough to allow an effective recovery of the animal but is short enough to limit the selection of resistance in food borne and/or commensal bacteria.

50. "Off label use" (off label use) of veterinary medicinal products:

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

52. 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. Non-therapeutic use of antibacterials should be discouraged.

Recording

53. Veterinarians should refer to recording information as covered in "Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993". Records on medication should be kept for at least two years and in conformity with national legislation. In addition, records should:

- specify the antimicrobial susceptibility testing done
- allow the investigation of adverse reactions to antimicrobial treatment, including lack of response due to antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities

54. Veterinarians should also periodically review farm records on antibacterial use

Training

55. Veterinary professional organisations should participate in the training programmes as defined in B 10.

RESPONSIBILITIES OF PRODUCERS

56. 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 in undertaking these duties. All people involved with food-producing animals have an important part to play in ensuring the responsible use of antimicrobials.

57. Efforts should be made to ensure that environmental contamination both by antimicrobials and by resistant bacteria is kept to a minimum.

58. 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 control 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 follow all provisions of the product label or prescription issued by the veterinarian.
- to use antimicrobial agents in the species, for the uses and at the doses on the approved/registered labels and in accordance with product label instructions or the advice of a veterinarian familiar with the animals and the production site;
- to isolate sick animals, when appropriate, to avoid the transfer of resistant bacteria;
- to comply with the storage conditions of antimicrobials in the rearing unit according to the provisions of the leaflet and package insert;
- 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 dispose of surplus antimicrobials, under safe conditions for the environment. Partially used medicines should only be used within the expiry date, for the condition for which they were prescribed and, if possible, in consultation with the prescribing veterinarian.

- to maintain all the laboratory records of bacteriological and susceptibility tests. These data should be made available to the veterinarian in charge of treating the animals in order to optimise the use of antimicrobials in that unit.
- to keep adequate records of all medicines used, including the following:
  - name of the 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
  - diagnosis / clinical conditions treated
  - quantity of the antimicrobial agent administered
  - withdrawal periods
  - result of laboratory tests
  - effectiveness of therapy
  - to inform the veterinarian in charge of the unit of recurrent disease problems

CONCLUSIONS

59. Antimicrobial agents are very important tools for controlling a great number of bacterial diseases in both animals and man. It is vital that all countries put in place the appropriate systems to ensure that antimicrobials are manufactured, marketed, distributed, prescribed, supplied and used responsibly, and that these systems are adequately audited.

60. This document is designed to provide the framework that countries should put in place in accordance with their possibilities 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 therein.

61. The continued availability of veterinary medicines, which are essential for animal welfare and 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 antimicrobial 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: harmonisation of national antimicrobial resistance monitoring and surveillance programmes in animals and in animal-derived food*. *Rev. sci. tech. Off. int. Epiz.,* 2001, **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: standardisation and harmonisation 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