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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 10 **CX/RVDF 01/10**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Thirteenth Session, 4-7 December 2001
Charleston, South Carolina, USA

DISCUSSION PAPER ON ANTIMICROBIAL RESISTANCE AND THE USE OF ANTIMICROBIALS IN ANIMAL PRODUCTION

INTRODUCTION

1. The relationship of the use of antimicrobials in food-producing animals and the emergence of resistant bacteria in the food chain is a concern and has been the subject of numerous national and international consultations ([1],[2],[3],[4]). The issues relating to antimicrobial[5] resistant bacteria in animals are discussed internationally by veterinarians, microbiologists and epidemiologists primarily through the OIE (Office International des Epizooties), the WHO (World Health Organization), FAO (Food and Agriculture Organization), VICH (Veterinary International Cooperation on Harmonization), the CODEX Committee on Residues of Veterinary Drugs in Foods (CCRVDF), the CODEX Committee on Food Hygiene (CCFH), and the *Ad hoc* Intergovernmental CODEX Task Force on Animal Feeding (ITFAF). Aspects relating to the medical impact in humans of antimicrobial use in animals have also been considered by the WHO. A chart of ongoing activities of these key international organizations is provided in Appendix A.

2. The 12th Session (March 2000) of the CCRVDF agreed that the United States, with the assistance of a drafting group (Australia, Brazil, Canada, Costa Rica, Denmark, Finland, Germany, Thailand, United Kingdom, OIE, WHO, European Community, International Federation for Animal Health (IFAH), Consumers International) would prepare a discussion paper for consideration by the next session taking into account work of other international organizations and CODEX committees in this area. The paper would consider all aspects of antimicrobial resistance relevant to the work of the CCRVDF and identify specific areas for further action, as required. The CCRVDF also agreed that the drafting group would consider development of a code of practice

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1 EU-conference "The Microbial Threat" Workshop no. 3. 1998-Sep-08. http://www.microbial.threat.dk

2 The Medical Impact of the Use of Antimicrobials in Food Animals. Report of a WHO Meeting. Berlin, Germany, 13-17 October 1997: http://www.who.int/emc-documents/antimicrobial_resistance/whoemczoo974c.html

3 Use of Quinolones in Food Animals and Potential Impact on Human Health, Geneva, Switzerland, 2- 5 June 1998: http://www.who.int/emc-documents/ zoonoses/ whoemczdi9810c.html

4 Office International des Epizooties, Press Release of 21 December 2000 ; Guidelines for the Control of Antimicrobial Resistance. http://www.oie.int/eng/press/a_001221.html

5 Antimicrobial agents or antimicrobial(s) refers to naturally occurring, semi-synthetic or synthetic substances which exhibit antimicrobial activity (destroy or inhibit the growth of other microorganisms). The term antimicrobial(s) comprises antibiotics, which refer to substances produced by or derived from microorganisms.

for the containment of antimicrobial resistance in the discussion paper.[6] This discussion paper provides an overview of issues concerning antimicrobial resistance relevant to the work of the CCRVDF. In addition, the paper proposes a draft Code of Practice for the Containment of Antimicrobial Resistance. The proposed code of practice uses as its starting point the OIE Guideline for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine[7]. The primary objective of the OIE guideline was to define the responsibilities of the authorities and stakeholders with regard to the use of antimicrobials in food-producing animals. The continued efforts of all of the involved international organizations will be necessary in order to effectively and expeditiously address the problem of antimicrobial resistance.

SCOPE

3. This paper considers antimicrobial resistance in the context of the international responsibilities of the CCRVDF. The paper also proposes a draft Code of Practice to Minimize and Contain Antimicrobial Resistance of potential consequence to human health that may be transferred through food. The future containment of antimicrobial resistance will require a coordinated multidimensional approach between the relevant CODEX committees (CCFH, CCRVDF, the *Ad hoc* Intergovernmental CODEX Taskforce on Animal Feeding, and the CODEX Committee on Pesticide Residues (CCPR). The document also highlights possible areas for further action by the CCRVDF related to antimicrobial resistance.

BACKGROUND INFORMATION

The Problem of Antimicrobial Resistance[8]

4. Antimicrobial agents are extensively used in human and veterinary medicine for treatment of infectious diseases and are also used to promote growth in animals. Without these drugs many infective diseases would be untreatable. In recent years the efficacy of human antimicrobial therapy has been challenged by the emergence of different resistant bacterial pathogens like vancomycin-resistant *Enterococci*, methicillin-resistant *Staphylococcus aureus*, and multiresistant *Mycobacterium tuberculosis.* The primary impact of resistance to antimicrobials is failure of empirical therapy of bacterial infections. This may lead to an increase in morbidity and mortality and hence prolonged suffering of infected patients and subsequent increase in costs for the public health sector.

5. Resistant bacteria represent a problem both in the community and in the hospitals. Nosocomial infections represent a special problem. In acute and chronic care facilities, transmission of bacteria from patient to patient can be high and outbreaks of inter-human transferred resistant bacteria may occur. Factors predisposing to this transmission include the severity of underlying illness, length of stay in the facility, and intensity and duration of exposure to antimicrobials. Nosocomial infections with resistant bacteria can have severe outcomes, including treatment failures and fatalities. In hospitals, multi-resistance in *Staphylococci, Enterococci, Pseudomonas* and a number of Enterobacteriaceae e.g., *Klebsiella* spp. and *Enterobacter* is the cause of serious problems. Inter-human spread of resistant pathogenic bacteria is also a problem in the community and includes bacterial pathogens like *Pneumococci, Staphylococci, Haemophilus influenzae, Haemophilus gonococci, Haemophilus meningococci, and Mycobacterium tuberculosis.*

6. Antimicrobial resistance in commensal and other non-pathogenic bacteria can also affect human health.

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6 ALINORM 01/31, paras. 33-38.

7 The Office of International Epizootics Guideline for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine, Office of International Epizootics *Ad hoc* Group on Antimicrobial Resistance.

8 The background information for this paper was adapted from the Joint FAO/WHO Food Standards Program Codex Committee on Food Hygiene, Thirty-second Session, Washington, D.C., 29 November - 4 December, Discussion Paper on Antimicrobial Resistant Bacteria in Food. Prepared by the Delegation of Denmark with assistance of Brazil, Canada, France, Finland, Hungary, Iceland, Netherlands, Norway, Sweden, United Kingdom, and the United States of America.

It is well known that resistant commensal organisms sometimes cause opportunistic infections, e.g. during surgery, when for instance immunocompromised patients are treated with an antimicrobial agent. The knowledge concerning antimicrobial resistance gene transfer in natural environments like food matrices and the digestive tract is relatively limited and it is difficult to estimate the significance of this problem for human health. However, transfer of resistance-genes between different genera has been documented in the gastrointestinal tract of animals and humans.

7. Animals serve as reservoirs for food borne pathogens, including *Salmonella* and *Campylobacter*. Antibiotic resistant food borne pathogens may be present in or on animals as a result of drug use in animals. These resistant food borne pathogens may contaminate a carcass at slaughter and can be transmitted to humans through consumption and handling of contaminated food. When these resistant bacteria cause an illness that needs treatment, medical therapy may be compromised if the pathogenic bacteria are resistant to the drug(s) used for treatment. In industrialized countries, the food borne pathogens, *Salmonella* and *Campylobacter*, are infrequently transferred from person to person. In these countries, epidemiological data have demonstrated that a significant source of antibiotic resistant food borne infections in humans is the acquisition of resistant bacteria originating from animals that is transferred on food. ([9],[10],[11])

8. The use of antimicrobials for growth promoting purposes in food-producing animals represents a special problem when it includes classes of antimicrobials that are used or are likely to be used for treatment of humans or animals or that are known to select for cross-resistance to antimicrobials used in human medicine. Examples of cross-resistance between different classes of antimicrobials used for both growth promotion and human treatment include tylosin/erythromycin (macrolides), virginiamycin/pristinamycin (streptogramins) and avoparcin/vancomycin (glycopeptides) and avilamycin/ everninomycin.

Antimicrobial Susceptibility and Resistance Transfer

9. The clinical definition of a resistant versus a sensitive microorganism is associated with the ability of a drug to be effective in the treatment of a specific infection. The susceptibility of a bacterium to an antimicrobial is a quantitative characteristic, usually expressed as the minimum inhibitory concentration (MIC), which denotes the lowest concentration of the specific antimicrobial that inhibits growth of the tested bacteria under standardized conditions in the laboratory. Different expert groups have suggested breakpoints for classification of different pathogenic bacteria as resistant or susceptible. These breakpoints support physicians and veterinarians in their choice of antimicrobials. Many antimicrobials are derived from microorganisms, and consequently resistance to these antimicrobials is a naturally occurring phenomenon. Microorganisms that initially lack a target site for an antimicrobial drug are referred to as being naturally or intrinsically resistant.

10. Microorganisms can acquire antimicrobial resistance: Changes in the DNA (mutations) or uptake of foreign DNA can change the susceptibility of a microorganism to an antimicrobial agent.

11. Mutations, which are naturally occurring in the genome, are one mechanism for acquisition of resistance in a microorganism. Another important way of acquiring resistance is the uptake of foreign DNA mediating resistance. Nature has developed different systems for transfer of genes between bacteria (conjugation, transformation, transduction, and transposition) and these mechanisms have proven effective in the promotion of resistance genes. Thus, the different resistance genes are shared by a number of various bacteria. Mobile genetic

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[9] Threlfall E, Frost J, Ward L, and Rowe B. Increasing spectrum of resistance in multi resistant *Salmonella typhimurium*. Lancet 347:1053-1054, 1996.

[10] Harris N, Weiss N, Nolan C. The role of poultry and meats in the etiology of *Campylobacter jejuni/coli enteritis*. Am J Pub Health 76(4):407-411, 1986.

[11] Tauxe RV. Epidemiology of *Campylobacter jejuni* infections in the United States and other industrial nations. In: Nachamkin I, Blaser MJ, Tompkins LS, Eds. *Campylobacter jejuni*: Current and Future Trends. American Society for Microbioloogy, Washington, D.C., pp. 9-12, 1992.

elements often carry several resistance genes, and consequently the uptake of a single mobile genetic element may confer resistance towards several antimicrobials at the same time. Multiresistant bacteria represent a special problem because the use of one antimicrobial can select for several resistance genes, a phenomenon referred to as co-selection of resistance.

12. Bacteria proliferate by division and this means that bacteria can inherit their resistance from their ancestors. In environments with antibiotics, resistant bacteria can disseminate very quickly because of their selective advantage. It is generally accepted that all antimicrobials selects for bacteria that are resistant, and it has furthermore been established, that there is an association, although complex, between the use of antimicrobials and the occurrence of resistant bacteria. Currently prudent use of antibiotics seems to be the main tool for preserving the effectiveness of antimicrobials.

Activities to Date

13. Soon after livestock producers began using antimicrobials in food-producing animals, scientists began studying the possible effects of long-term use of antibiotics. The following is a review of the key studies and reports to date.

1960 Netherthrope Commmittee

14. It was formed in the UK to consider possible human health implications from the use of subtherapeutic antibiotics in food-producing animals and concluded that there was no evidence of a human health hazard associated with the use.

1969 Swann Committee

15. Also formed in the U.K., the committee reported no hazard to humans or animals from, the use of antibiotics in poultry or swine. However, it linked an outbreak of salmonellosis in humans to the therapeutic use of antibiotics in sick calves. The committee recommended:

- Antibiotics used in animals should be divided into “feed” or “therapeutic” classes.
- The “feed” antibiotics class should not include drugs used therapeutically in humans or animals.
- “Therapeutic” antibiotics should be available only by prescription.

1970 US Food and Drug Administration (FDA) Task Force

16. The task force report, “The Use of Antibiotics in Animal Feeds,” concluded:

- The use of subtherapeutic amounts of antimicrobials favored the selection and development of resistant bacteria.
- Animals receiving antimicrobial treatment may serve as a reservoir of antibiotic resistant pathogens and can produce human disease.
- The prevalence of multi-resistant bacteria in animals has increased due to the use of antimicrobials.
- Resistant bacteria are present in meat and meat products.
- There has been an increase in the prevalence of antimicrobial resistant bacteria in man.

1988 U.S. Institute of Medicine Review

17. In 1988, the Institute of Medicine (IOM) reviewed all the information about the antibiotic resistance issue available. An expert Committee was convened to determine the human health risks associated with the practice of feeding subtherapeutic level of penicillin and tetracyclines to animal for growth promotion, feed efficiency, and disease prevention. In the report, “Human Health Risks with the Subtherapeutic Use of Penicillin

or Tetracyclines in Animal Feed," the Committee developed a risk-analysis model, using data only on Salmonella infections that resulted in human death. The Committee found a considerable amount of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard, but did not find data demonstrating that use of subtherapeutic penicillin or tetracycline directly caused a human to die from salmonellosis. The Committee strongly recommended further study of the issue.

1995 ASM Report

18. The American Society of Microbiology (ASM), which includes members who specialize in medical and animal microbiology, issued a report in 1995 that cited grave concerns about both human and animal antibiotic use and the rise in antimicrobial resistance. The report advocated a significant increase in resistance monitoring in the U.S., more education about the use and risks of antimicrobials, and more basis research designed to develop new antimicrobials and vaccines and disease prevention measures. The report criticized overuse of antibacterials in human medicine, both also pointed out the large use in food production, which was partly attributed to the consolidation of farms to facilities with large numbers of confined animals. The report made it clear that the antibiotic resistance problem is global.

1997 WHO Meeting

19. In 1997, the World Health Organization (WHO) held a meeting of experts in Berlin, Germany to review the question of whether the use of antimicrobials in animals leads to antimicrobial resistance in humans. The experts sought to define potential medical problems that could arise from antimicrobial use in food-producing animals and to make recommendations to address the issue. The group of experts recommended against using antimicrobials for growth promotion, if those antimicrobials are also used in human medicine or can induce cross-resistance to antimicrobials used for human medical therapy. The group also recommended that research be conducted on non-antimicrobial growth-promoters and urged that the risk to human health from use of antimicrobials in food animals be accurately assessed. The group called for enhanced monitoring of resistance among isolates of enteric bacteria from food animals and food of animal origin. In addition, the group recommended managing risk at the producer level through the prudent use of antimicrobials.

1998 OIE Study

20. The role of international trade in animals, animal products and feed in the spread of transferable antibiotic resistance and possible methods for control of the spread of infectious agent resistance factors.

21. The results of an early investigation conducted by the OIE into existing activities and capacities in the detection and control of antibiotic resistance of the 50 European countries were presented in 1998. They showed that additional efforts should be made in order to develop official antimicrobial resistance surveillance/monitoring programs and to improve the harmonization of laboratory methodologies, which in turn will improve the reliability and comparability of generated resistance data. The study also revealed that risk analysis was not always used when sanitary measures were considered by countries. ([12])

1998 WHO Meeting

22. In June 1998, the WHO held another meeting, this time in Geneva, Switzerland to specifically address the use of quinolones in food-producing animals. The participants agreed that the use of antimicrobials will cause resistance to develop and that there is a potential human health hazard from resistant *Salmonella*, *E. coli*, and *Campylobacter* organisms transferred to humans through the food supply. The experts also concluded that more information was needed to accurately assess the risk associated with the use of these products in animals,

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12 Comprehensive reports on technical items presented to the International Committee or to Regional Commissions (1988). Office of International Epizooties.

but supported the use of quinolones to treat sick animals where necessary.

1999 EU Expert Committee Reports

23. The Scientific Steering Committee of the European Commission published a report on antimicrobial resistance in May 1999. The Committee concluded that actions should be taken promptly to reduce the overall use of antimicrobials in a balanced way in all areas. Four primary recommendations were made: 1) antimicrobials should be used prudently, 2) infections should be prevented and resistant organisms contained, 3) research for new modalities of prevention and treatment of infections should be undertaken and 4) the effects of interventions should be monitored and evaluated. On the basis of on-going work of this Committee and other information available, the agriculture ministers in the EU voted in December 1998 to ban four antibiotics that are widely used at subtherapeutic levels to promote animal growth. The ban on using bacitracin zinc, spiramycin, tylosin, and virginiamycin in animal feed became effective for the fifteen member states of the EU on July 1, 1999.

24. The Committee for Veterinary Medicinal Products (CVMP) recommended in its report in July 1999 that models should be developed to assess the risks of antibiotic resistance occurring in animals and its potential transfer to man. The CVMP also recommended pre-marketing assessment of the potential of antimicrobials to cause resistance development, development of strategies to maintain efficacy of veterinary products while reducing the potential risk to public health and development of prudent use policies. Based on this report the strategic plan to develop guidelines was adopted in the CVMP in January 2000.

1999 OIE International Conference on Antimicrobial Resistance

25. The Office International des Epizooties (OIE) held an international conference in March 1999 on antimicrobial resistance to promote exchange among stakeholders and decision-makers in the human and animal medical fields. The conference stressed the need to follow risk analysis procedures and to apply scientific principles when managing antimicrobial resistance. The conference served as a forum for countries to report on current regulatory activities and capacities in the detection and quantification of antimicrobial resistance. A second conference is planned for October 2001 to review progress achieved in understanding the development of antimicrobial resistance in humans and animals, problems encountered in both human and veterinary medicine, and actions taken by regulatory authorities and others for the containment of antimicrobial resistance.

1999 Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR)

26. The JETACAR was appointed in 1998 and charged by the Australian Minister for Health and Family Services and the Minister for Primary Industries and Energy to examine the issue of antimicrobial resistance from a scientific perspective. The Committee was made up of experts from public health, human and veterinary medicine, molecular biology and the primary industries. The Committee reviewed the scientific evidence on the link between the use of antibiotics in food-producing animals, the emergence and selection of antibiotic-resistant bacteria and their spread to humans, and made recommendations for the appropriate future management of antibiotic use in food-producing animals. Key stakeholders were invited to provide input in the form of scientific data during the Committee deliberations and also to the draft report, which was published in March 1999. The final report was issued in September 1999. The JETACAR concluded that there is a hazard to food safety and human health from the use of antibiotics in food-producing animals, which must be weighed against the value of antibiotics to veterinary medicine, food productivity and animal welfare.

27. The Commonwealth Government Response to the JETACAR Report was published in August 2000 by the Australia Departments of Health and Aged Care and Agriculture, Fisheries and Forestry. In its response, the Commonwealth Government acknowledges the threat from antibiotic resistant organisms to human health and strongly supports the intent of the JETACAR recommendations. The government response stresses the need for a coordinated and balance approach to better manage the use of antibiotics in humans and food-producing animals. The Commonwealth Government has agreed to establish two groups to implement the plan, an Expert

Advisory Group on Antibiotics under the auspices of the National Health and Medical Research Council and an Interdepartmental JETACAR Implementation Group to oversee and coordinate the continuing Government response to the JETACAR.

2000 WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food

28. The WHO held an expert consultation in June 2000 with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties to develop global principles for the containment of antimicrobial resistance in food-producing animals. The purpose of the expert consultation and development of global principles is to minimize the negative public health impact of the use of antimicrobial agents in food-producing animals while at the same time providing for their safe and effective use in veterinary medicine. The Principles provide a framework of recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of human health. The Principles are part of a comprehensive WHO global strategy for the containment of antimicrobial resistance. The Principles strengthen and endorse earlier WHO recommendations such as the need to terminate the use of antimicrobial growth promoters pending comprehensive human health safety evaluations, and the need to establish surveillance systems on antimicrobial consumption.

2000 OIE Expert Group on Antimicrobial Resistance

29. At the request of the OIE International Committee, an OIE Expert Group on Antimicrobial Resistance was established in January 2000. With the participation of the FAO and WHO, the OIE Expert Group has elaborated the following five guidelines on antimicrobial resistance:

1. Risk assessment methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin;
2. Prudent and responsible use of antimicrobial agents in veterinary medicine;
3. Monitoring of quantities of antimicrobials used in animal husbandry;
4. Harmonization of national antimicrobial resistance monitoring and surveillance programs in animals and in animal derived foods;
5. Standardization and harmonization of laboratory methodologies used for the detection and quantification of antimicrobial resistance.

PROPOSED CODE OF PRACTICE TO MINIMIZE AND CONTAINANTIMICROBIAL RESISTANCE

30. The proposed Code of Practice to Minimise and Contain Antimicrobial Resistance (See Appendix B) uses as its starting point the OIE Guideline for the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine. A number of codes of practice relating to the use of antimicrobials and the conditions were taken into consideration in the elaboration of the OIE guideline. The primary objective of the OIE Guideline is to define the responsibilities of the authorities and stakeholders with regard to the use of antimicrobials in food-producing animals. It defines the respective responsibilities of authorities and groups involved in the registration, production, control, distribution and use of antimicrobials in food-producing animals, including the national competent authorities, the veterinary pharmaceutical industry, veterinarians, pharmacists, and livestock producers.

SPECIFIC AREAS FOR FURTHER ACTION

31. The multidimensional nature of antimicrobial resistance will continue to require a coordinated approach among all relevant international organizations in order to develop effective science-based risk assessment policies. The CCRVDF needs to work closely with other relevant international standard-setting and regulatory bodies in order to take into account various international regulatory initiatives and developments and to ensure that its outputs are consistent with existing international conventions and agreements. Such cooperation is also important to minimize duplication of effort. Close coordination between the CCFH and the CCRVDF, and

potentially the CCPR, in accordance with their respective terms of reference, will also be essential.

32. Within the Codex organization itself, there are a number of groups that currently are considering the public health implications of using antimicrobial agents in food-producing animals. On-going Codex efforts have included the activities of the CCFH, the ITFAF, the CCRVDF, and the JECFA. Approaches to understanding the public health significance of antimicrobial resistance within each of these groups has tended to focus on the professional disciplines reflected by the traditional membership of these groups: microbiological risk profiles in CCFH, safety of residues in CCRVDF and JECFA, and feeding practices and the manufacture of animal feeds in ITFAF.

33. The CCFH, due to its recognized expertise in food hygiene in general and in food microbiology in particular, has the specific duty to propose any measures likely to improve the microbiological quality of animal-derived food. These measures are expected to decrease the burden of bacteria, sensitive or resistant to antimicrobials, in animal-derived food. CCFH should also prioritize pathogens or pathogen-commodity combinations, including antimicrobial-resistant pathogens, for microbiological risk assessments.

34. CCRVDF should be involved in reducing the prevalence of bacteria resistant to antimicrobials in animal-derived food. CCRVDF is composed of people having responsibilities in veterinary medicinal product management in general and in veterinary medicinal product registration in particular. CCRVDF has experience with the issue of antimicrobial resistance in establishing Marls for antimicrobial residues and is currently basing its work on the risk analysis approach including the setting of science-based risk assessment policy. On this basis, CCRVDF should be responsible for the following:

- developing a risk assessment policy regarding animal bacteria resistant to antimicrobials

- identifying the priority risk assessments to be carried out by an appropriate expert group in conjunction with CCFH, and

- considering the outcome of these risk assessments for proposing recommendations likely to help CODEX member states in their risk management responsibilities.

35. In keeping with the CODEX Alimentarius Commission's (CAC) Draft Strategic Framework,[13] the CCRVDF should include in its considerations the widest possible application of risk analysis based on CODEX principles. Currently, the CAC gives high priority to the establishment of sound working principles for the application of risk analysis at the national and international levels.

36. The Code of Practice to Minimize and Contain Antimicrobial Resistance (Appendix B) provides additional guidance for the responsible and prudent use of antimicrobials in food-producing animals and is intended to be used in conjunction with the current "Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38." The draft Code of Practice to Minimize and Contain Antimicrobial Resistance describes a multifaceted approach to the complex problem of minimizing the emergence of antimicrobial-resistant bacteria and resistance determinants in animals and their subsequent spread to humans through the food supply.

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[13] ALINORM 01/6, CODEX Alimentarius Commission, Twenty-fourth Session, 2-7 July 2001, International Conference Center, Geneva, Switzerland, Consideration of the Draft Strategic Framework Proposed Draft Medium Term Plan 2003-2007, paragraphs. 9-11.

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Appendix A

Key International Activities on Antimicrobial Resistance

International Organization	Activities on Resistance
World Health Organization	• Containment of antimicrobial resistance in food-producing animals • Prudent use of antimicrobials in food-producing animals • Research • Development of recommendations on surveillance programs, antimicrobial use in aquaculture, monitoring of drug use in food-producing animals • Planning to address the impact on animal husbandry of elimination of growth promotion use of antimicrobials
OIE Ad Hoc Expert Group on Antimicrobial Resistance	• Risk assessment techniques • Standardization and harmonization of laboratory methodologies • Harmonization of national antimicrobial resistance monitoring programs • Guidelines on prudent use of antibiotics in animal husbandry • Guidelines on monitoring the quantity of antibiotics used in animal husbandry
OIE Prudent Use Principles	• Maximize therapeutic effect while minimizing development of resistance • Antibiotics are a necessary part of a good management strategy • Prudent use guidelines should have practical application on a global scale • Assume that implementation of prudent use guidelines and commitment to them by veterinarians will remove the risk of over-prescribing

CODEX Committee on Food Hygiene	• Developed discussion paper: Risk profile on antimicrobial resistant bacteria in food (risk profile includes a description of a microbiological food safety problem plus a situation analysis to determine the size and nature of the problem and what action(s) may be necessary, including a risk assessment.) • Identifying the microbiological hazard(s) causing the problem • Determining the source of the hazard • Identifying mechanisms for the development of resistance • Identifying reservoirs for resistant bacteria • Identifying factors that may contribute to spread of resistant bacteria • Determining the types and severity of adverse effects and the populations affected
CODEX Committee on Residues of Veterinary Drugs in Foods	U.S. is leading a drafting group in defining the scope of work for this committee Working group will also prepare a draft code of practice on prudent use
Ad hoc Intergovernmental CODEX Taskforce on Animal Feeding	Addressing aspects of animal feeds and feeding practices that are important for food safety, including antimicrobial resistance
VICH Working Group on Antimicrobial Resistance	Expert working group is developing guidance on studies on resistance in food animals and prudent use labeling of antimicrobial products

Appendix B

PROPOSED DRAFT CODE OF PRACTICE TO MINIMIZE AND CONTAIN ANTIMICROBIAL RESISTANCE

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 development of antimicrobial resistance that has the potential to adversely impact the safety of foods produced from such treated or exposed animals and to ensure the safe and effective use of antimicrobials in veterinary medicine. It defines the respective responsibilities of authorities and groups involved in the registration, production, control, distribution and use of veterinary antimicrobials such as national competent authorities, the veterinary pharmaceutical industry, veterinarians, pharmacists, and food animal producers.

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. 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 a set of practical measures and recommendations intended to prevent and/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 with their resistance determinants bacteria within animal populations, to maintain the efficacy of antimicrobial agents used in food-producing animals
- prevent or reduce the transfer of resistant bacteria or resistance determinants from animals to man, to maintain the efficacy of antimicrobial agents used in human medicine
- prevent the contamination of animal derived food with antimicrobial residues which exceed the established MRL
- maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals
- comply with the ethical obligation and economic need to keep animals in good health

5. 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 when disease problems become evident
- aims to limit the use of antimicrobial agents to their approved and intended uses 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)
- does not include the non-therapeutic use of antimicrobials that belong to classes of antimicrobial agents used (or submitted for approval) in humans in the absence of an 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

6. 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. National governments should adopt a proactive approach to reduce the need for antimicrobials in food-producing animals and their contribution to antimicrobial resistance to ensure their prudent use (including reducing overuse and misuse) as an element of a national strategy for the containment of antimicrobial resistance.

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

8. 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 consumerresulting 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. If dose ranges or different durations 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. No antimicrobial should be administered to animals unless it has been evaluated and authorized for such use by the relevant authorities. 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.

9. Countries without the necessary resources to implement an efficient registration 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 registration 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.

10. 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 trade, distribution and use of illegal and counterfeit products.

11. A risk-based evaluation of the potential human health effects for uses of antimicrobial drugs in food-producing animals should be conducted, including currently approved products. In the evaluation of currently approved products, priority should be given to those products considered most important in human medicine. Characterization of the risk should include consideration of the importance of the drug or members of the same class of drug to human medicine, the potential exposure to humans from antimicrobial-resistant bacteria and their resistance genes from food animals, as well as other appropriate scientific factors. Those antimicrobials judged to be essential for human medicine should be restricted and their use in food animals should be justified by culture and susceptibility results.

Quality Control of Antimicrobial Agents

12. Quality controls should be carried out:

- in compliance with the provisions of good manufacturing practices
- to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs
- 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 in order to guarantee their safety and efficacy.

Control of the Therapeutic Efficacy

13. 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.

- Important pharmacodynamic information may include:

    - mode of action
    - minimum inhibitory and bactericidal concentrations
    - time or concentration-dependent activity
    - activity at the site of infection

- 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

- 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 antibiotics responsible for additive or synergistic effects at the site of infection throughout the treatment period)

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

- The ability of the antimicrobial agent to select for resistant bacteria *in vitro* or *in vivo* should be assessed. The design of *in vivo* studies is currently under development.
- In certain cases, preclinical trials should evaluate not only bacteria of target animals for resistance, but also the 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 that is relevant to assessing the potential to select for antimicrobial resistance in the target animal species when the product is used under the intended conditions of use.
- Preclinical and clinical data should, in certain cases, be used to evaluate not only pathogenic bacteria of target animals for resistance, but also the impact of the antimicrobial use on food borne and/or commensal (indicator) bacteria.

14. However, further research is needed to develop specific studies that are appropriate for evaluating the potential for antimicrobial drug products to select for resistance. In the interim, appropriate information should be provided to support an adequate assessment of the safety of antimicrobial products being considered for registration 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 in the pathogens of human health concern (baseline determination)

15. 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.

Establishment of ADIs (Acceptable Daily Intakes), MRLs (Maximum Residue Limits) and Withdrawal Periods for Antimicrobial Compounds

16. When setting ADIs and MRLs for antimicrobial substances, the safety evaluation should, for this class of substances, also include the potential biological effects on the human intestinal flora. Using in vitro and/or in vivo tests and/or data originating from human medicine, an assessment of the capability of antimicrobial residues, ingested by the consumer, to disturb the human intestinal flora by selecting resistant bacteria and /or weakening its barrier effect against the colonisation of pathogenic bacteria should be undertaken.

17. The establishment for each antimicrobial agent of an acceptable daily intake (ADI), and a maximum residue limit (MRL) for each animal derived food, 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.

18. 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

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

Protection of the Environment

20. An assessment of the impact of the proposed antimicrobial use on the environment should be carried out. 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

21. 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
- particular precautions for the proper disposal of un-used products

23. The conditions of prudent use of an antimicrobial agent in veterinary medicine should be based on a safety evaluation, which includes a consideration of the importance of the drug or other antimicrobial agents belonging to the same therapeutic class, in human or veterinary medicine. Antimicrobials that are considered important to treat critical diseases in humans should only be used in animals when alternatives are either unavailable or inappropriate. Consideration should be given to providing the veterinarian or user appropriate prudent use guidance with the product.

24. For certain antimicrobial drugs, any information on conditions of use relevant to the potential for selection of resistance should be included.

Post-Marketing Antimicrobial Resistance Surveillance

25. There should be a structured approach to the investigation and reporting of the incidence and prevalence of resistance.

26. 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.

27. Non-specific surveillance

- 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.

28. Specific surveillance

- The surveillance of animal bacteria resistant to antimicrobial agents is recommended l. 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 antimicrobial 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”).

- This epidemiological surveillance of antimicrobial resistance should be accompanied by a continuous survey on the amounts of antimicrobial agents used by veterinarians and other authorized users in order to encourage the most appropriate prescription of these medicinal products.

- If justified by the results of this post registration surveillance of antimicrobial resistance, whether specific or not, the conditions of use of the antimicrobial agents in veterinary medicine should be modified.

Distribution of the Antimicrobial Agents Used in Veterinary Medicine

29. 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

Control of Advertising

30. 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 restricted to the authorized professionals, according to 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 Antibiotic Users

31. 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

32. 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 registration 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 etc.).

RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY

Marketing Authorization of Antimicrobials for Food-Producing Animals

33. 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.

34. 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

- 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

35. 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

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

- to participate in the training programmes as defined under "Training of Antibiotic Users"

Research

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

- to contribute to the research effort as defined under "Development of Research"

RESPONSIBILITIES OF PHARMACISTS AND/OR DISTRIBUTORS

38. 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 "Responsibilities of Veterinarians – Recording")

39. Pharmacists should reinforce the guidelines on the responsible use of antimicrobials.

40. 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

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

RESPONSIBILITIES OF VETERINARIANS

42. The use of antimicrobials is no substitute for good management practices and the veterinarian's prime concern is to encourage good farming practice in order to minimise the need for antimicrobial use in food-producing animals.

43. In the framework of good management practice 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.

44. 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

45. 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.

46. The responsibilities of veterinarians in this area are the following:

Use of Antimicrobial Agents When Necessary

47. 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.

48. 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 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 antibiotic profiles should be established before the commencement of treatment. Should a first line antibiotic 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

  In order to minimize the likelihood of antimicrobial resistance developing, it is recommended that antimicrobials 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 combinations of antimicrobial agents
  - the importance of the drug to human and/ or veterinary medicine. Antimicrobials, which are considered important to treat critical diseases in humans that may be compromised by antimicrobial use in food-producing animals, should not be intensively used when other therapies are available or appropriate.
  - the route of administration.

- Combinations of antimicrobials

  - Combinations of antimicrobials are used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.
  - Furthermore, 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.
  - On the other hand, a bad choice of a combination of antimicrobials may in certain cases lead to an increase of the selection of resistance.
  - 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 should check the ability of these antibiotics to reach the infection site under similar time and concentration conditions, to maintain effective therapeutic concentrations as long as is needed.

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.

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" (extra-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. 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.

Recording

53. All available information should be consolidated into one form or database for two years, such that this information should

- allow monitoring of the quantities of medication used
- contain a list of all medicines supplied to each livestock holding
- contain a list of medicine withdrawal periods and a system for allowing information to be updated
- contain a record of antimicrobial susceptibilities
- provide comments concerning the response of animals to medication
- 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

Labelling

54. All medicines supplied by a veterinarian should be adequately labelled with the following minimum information:

- the name of the owner/keeper or person who has control of the animal(s)
- the address of the premises where the animal(s) are kept
- the name and address of the prescribing veterinarian
- the date of supply
- the words for animal treatment only
- the words keep out of the reach of children
- the relevant withdrawal period even if it is nil

55. The label should not obscure the expiry date of the preparation or any important information supplied by the manufacturer.

Training

56. Veterinary professional organisations should participate in the training programmes as defined in "Responsibilities of the Regulatory Authorities – Development of Research".

RESPONSIBILITIES OF PRODUCERS

57. 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.

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

59. Food animal producers have the following responsibilities:

- to use antimicrobial products only when necessary and regard them as a complement to and not a replacement for good management, vaccination and farm hygiene;
- 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 only on veterinary prescription and according to the provisions of the

prescription;

- 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.

CONCLUSION

60. 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.