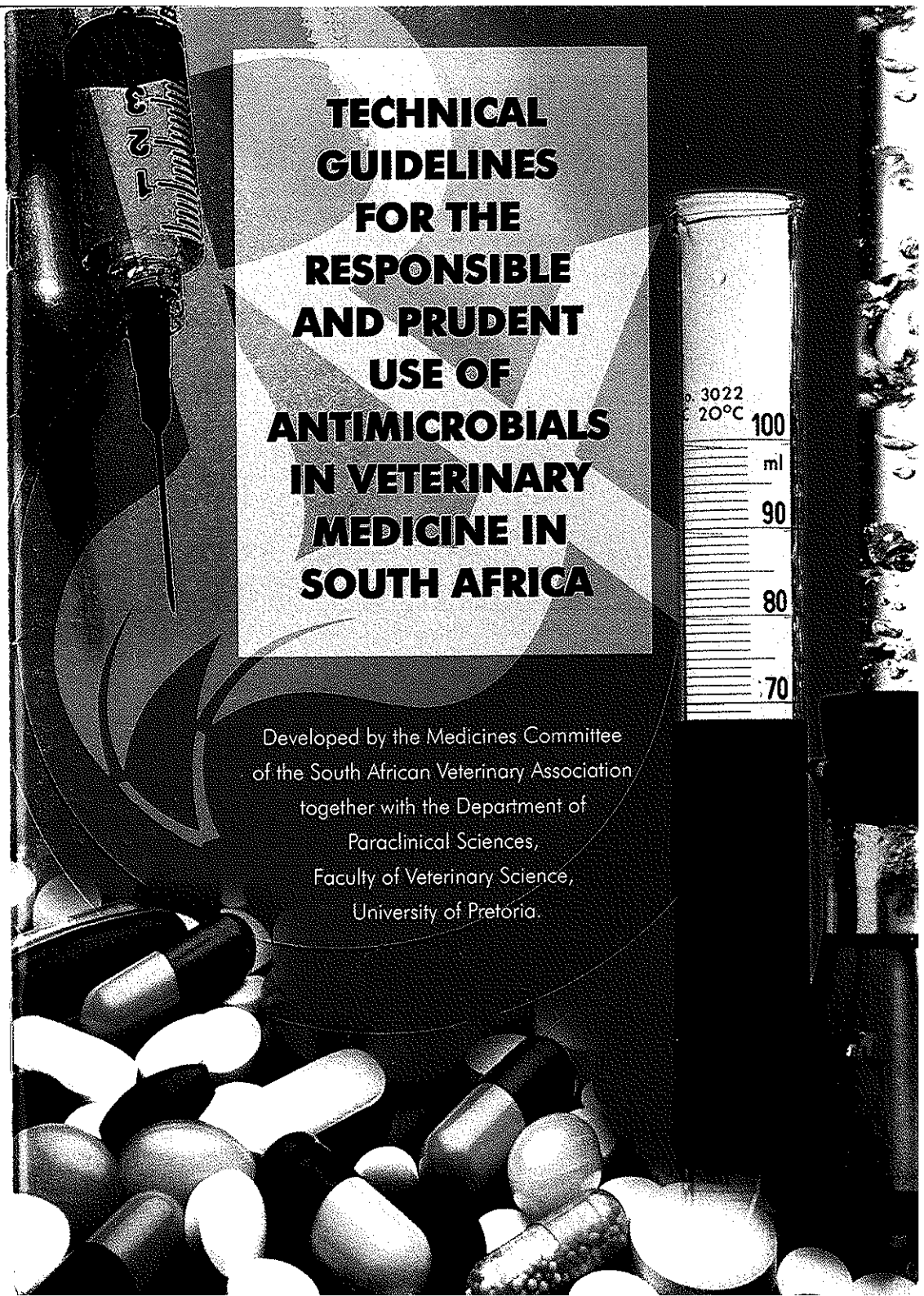

TECHNICAL GUIDELINES FOR THE RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIALS IN VETERINARY MEDICINE IN SOUTH AFRICA

Developed by the Medicines Committee
of the South African Veterinary Association
together with the Department of
Paraclinical Sciences,
Faculty of Veterinary Science,
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1. INTRODUCTION

1.1 Definition of an antimicrobial

An *antimicrobial* can be defined as any product of natural, semi-synthetic or synthetic origin, which as its primary activity either kills or inhibits the growth of microorganisms, in particular bacterial organisms. The treatment of disease using antimicrobial drugs exploits the differences in the structure or biochemical function between host and parasite to selectively target the causative agents of disease whilst causing little or no damage to the host. An *antibiotic* is a substance produced by a microorganism (i.e. a natural substance) that at low concentrations inhibit or kills other microorganisms[4].

1.2 Importance of antimicrobials in veterinary medicine

Antimicrobials are a highly effective tool used to control and treat infectious or contagious diseases caused by microorganisms. Their use in veterinary practice helps to ensure the health and well-being of livestock and companion animals. It also facilitates the production of meat, eggs and milk products that are safe for the consumer and for those concerned with their production.

1.3 Extent of use of antimicrobial agents in veterinary medicine

In veterinary medicine, antimicrobial drugs are used under the following circumstances[7]:

- Therapy – used in the presence of disease
- Prophylaxis – used for the prevention of disease
- Metaphylaxis – sick and healthy animals are treated simultaneously during an outbreak of disease in a group of animals

- Production enhancement in food-producing animals

The level of use of antimicrobial drugs must be considered in relation to the total consumption of all veterinary medicinal products.

1.4 Development of antimicrobial drug resistance[4]

Antimicrobial resistance is defined as occurring when the concentration of the antimicrobial drug required to inhibit or kill the microorganisms is greater than the concentration that can be safely achieved.

Resistance can be classified as either constitutive (inherent) or acquired.

Constitutive resistance occurs when bacteria lack the cellular mechanisms required for antibiotic action (e.g. inherent resistance of Enterobacteriaceae to penicillin G). Also, *in vitro* susceptibility may not always indicate *in vivo* susceptibility; as for example with gram-positive bacteria that are resistant to beta-lactam antibiotics because they lose their cell wall but subsequently persist in the body as L forms.

Acquired resistance is genetically based and can arise because of chromosomal mutation, or more importantly, through the acquisition of transferable genetic material. Mechanisms of acquired resistance include:

- Enzymatic inactivation of antibiotics
- Impermeability of bacteria
- Alteration of target receptors
- The development of bypass mechanisms in metabolic pathways
- Decreased accumulation of the drug by resistant cells
- The development of enzymes with low drug affinity

The use of antimicrobial drugs eliminates the susceptible bacteria in the host and spares the resistant ones. These resistant bacteria reproduce, resulting in a resistant population.

Chromosomal resistance

Chromosomal resistance is generally a minor problem. Chromosomal mutations tend to produce structural changes in the bacterial cell,

and resistance due to this mechanism is generally a gradual, stepwise process.

Mutations that result in antibiotic resistance are spontaneous events that occur independently of the presence of antimicrobials and are often associated with other cell changes that make the mutants less viable. Mutants are therefore diluted out from the population in the absence of antibiotic selection and the host defences kill many of them. Chromosomal resistance therefore emerges less frequently *in vivo* than *in vitro*. Low and intermittent drug dosage tends to favour the development of mutational resistance.

Examples of mechanisms by which chromosomal mutations determine antibiotic resistance include:

- Changing target sites such as chromosomes (e.g. streptomycin, erythromycin)
- Altering cell permeability (e.g. chloramphenicol, tetracyclines)
- Increasing production of inactivating enzymes (e.g. selection of stable mutants with derepressed beta-lactamase enzymes in gram-negative bacteria)
- Increasing production of competitive metabolites (e.g. sulfonamides)

Using combinations of antimicrobials will minimise the development of chromosomal resistance because the chance of two mutations occurring simultaneously in the same bacterium is the product of the chance of each mutation occurring alone.

Transferable drug resistance

Transferable resistance is of major significance and tends to code for enzymes that metabolise antibiotics. It is often high-level and all-or-none.

Transferable drug resistance may result in epidemic or infectious resistance and bacteria often develop resistance to several antibiotics at the same time by this mechanism. Genetic transfer may even result in resistance in the absence of selection by antimicrobial drugs, although this is quite uncommon.

Bacteria possess the remarkable ability to share genetic information within populations that will promote their survival in adverse environments. The genetic elements responsible for the transfer of antimicrobial resistance are the R plasmids. These consist of extra chromosomal circular DNA that replicate within the cell and are spread to other cells by one of the following mechanisms:

- Conjugation: A donor bacterium synthesises a sex pilus that attaches to a recipient bacterium in a mating process and transfers copies of plasmid-mediated resistance genes to the recipient. The donor retains copies of the plasmid, and the recipient now becomes a potential donor. This transfer may occur between bacterial strains of the same species, within species of the same genera. Or even between species belonging to different families. (This is the most common process of gene transfer.)
- Transduction: Plasmid DNA is incorporated by a bacterial virus and transferred to another bacterium (e.g. transfer of the beta-lactamase gene from resistant to susceptible staphylococci).
- Transformation: Naked DNA passes from one cell to another, altering the genotype of the transformed recipient cell (this method of transfer is not clinically important).

Plasmids possess regions that code for resistance to between 1 and 10 different antibiotics. They also have regions that code for the ability of bacteria to transfer genes by conjugation. They are relatively stably inherited, but are not required for the survival of the bacterium.

Transposons are short sequences of DNA that have the ability to move and integrate into foreign DNA sequences by nonhomologous recombination. They consist of an antimicrobial drug-resistance gene flanked by two insertion sequences. They are readily acquired by plasmids and may be readily incorporated into chromosomal DNA. This results in plasmids of very diverse origins possessing identical resistance genes. The transfer of transposons between plasmids in a cell and between chromosomes and plasmids, together with the interbacterial transfer of plasmids, can result in the rapid development of antimicrobial resistance in bacterial populations.

Although resistance has been identified in virtually every pathogenic

bacterial genus, not all bacterial species possess the same ability to develop acquired resistance to antimicrobial drugs. For example, many gram-positive bacteria, except for staphylococci, lack the ability to acquire R plasmids and hence lack the ability to develop transferable resistance. However, resistance has become a serious constraint in the treatment of diseases caused by Enterobacteriaceae and other gram-negative pathogens such as *Bordetella, Haemophilus, Pasteurella and Pseudomonas.*

The term cross-resistance describes the phenomenon by which bacteria acquire resistance to an antimicrobial drug indirectly through the development of resistance to another, often related, drug (e.g chromosomal resistance to gentamicin is associated with resistance to older drugs such as neomycin). This phenomenon is common in the macrolide group of drugs.

1.5 Potential risk to human populations

The effect of the use of antimicrobial drugs in veterinary medicine on human health is uncertain.

However, there are a number of potential risks that should be considered.

1. The transfer of resistant zoonotic bacteria to the human population through food of animal origin (e.g. *Salmonella* infections).
2. The transfer of resistance genes from nonpathogens (e.g. *E. coli*), acquired through food of animal origin, to human pathogens by means of R plasmids.
3. The alteration of human gastro-intestinal microbial flora through the ingestion of antimicrobial residues in food of animal origin by selecting for antimicrobial resistant bacteria and/or weakening the barrier effect of such flora against the colonisation of pathogenic bacteria.
4. The alteration of commensal bacterial populations through human contact with antimicrobial agents administered to animals

Evidence suggests that the use of antimicrobials in animals has selected for antimicrobial-resistant *Salmonella* serotypes. There has also been a rise in the number of fluoroquinolone-resistant *Campylobacter jejuni* isolated from live poultry, poultry meat and infected humans following the introduction of the fluoroquinolones

for use in poultry[6].

A reservoir of transferable resistance genes to glycopeptides, including vancomycin, has developed in the commensal enterococci of animals due to the use of avoparcin as a growth-promoting feed additive in animal husbandry. The extent to which this gene pool in animals contributes to the prevalence of glycopeptide-resistant commensal enterococci in humans has not been quantified. Glycopeptide-resistant enterococci cause serious infections in hospitalised immune-impaired patients. Due to the limited number of antimicrobials available for the treatment of these resistant enterococci, antimicrobials are being sought that have not been previously used in humans. This includes drugs that have been used as growth promotants in animals. Glycopeptide resistance genes could also be transferred to other gram-positive organisms, particularly multiresistant *Staphylococcus aureus*, for which vancomycin is the drug of last resort[6].

Multiresistant *Escherichia coli* have been selected by the use of broad-spectrum antimicrobials in livestock and humans. Certain *E. coli* are food-borne pathogens, for which therapy may be compromised by the development of resistant strains[6].

1.6 Current initiatives

A number of initiatives are currently underway to develop guidelines for the prudent use of antimicrobials. These include projects by the OIE, WHO in collaboration with the FAO, the WVA in collaboration with IFAP and COMISA and RUMA.

2 AIMS AND OBJECTIVES

The misuse of antimicrobial agents in veterinary medicine leads to an increased selection for resistant bacteria associated with animals and their spreading among animals and possibly to humans. It can shorten the effective life-span of antimicrobial agents and may lead to the restriction of the availability of antimicrobials for use in veterinary medicine, which would have serious health implications for animals and humans. Technical Guidelines for the prudent and responsible use of antimicrobial agents in veterinary medicine are intended as a set of recommendations and practical measures to promote the effective and safe use of these drugs,

which would minimise the selection for antimicrobial resistant bacteria in animals.

The aim of setting up such guidelines would be to maintain the efficacy of antimicrobial agents and ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals in order to:

- Comply with the ethical obligation and economic need to keep animals healthy
- Protect consumer health by ensuring the safety of food of animal origin
- Prevent/ reduce the transfer of resistant bacteria within animal populations, which would maintain the efficacy of antimicrobial agents used in livestock
- Prevent/ reduce the transfer of resistant bacteria or resistant genes from animals to man, which would maintain the efficacy of antimicrobial agents used in human medicine
- Prevent the contamination of animal-derived food with antimicrobial residues that may have a detrimental effect on human health

3 PRINCIPLES OF THE PRUDENT USE OF ANTIMICROBIALS IN VETERINARY MEDICINE

3.1 Basic assumptions

The prudent use of antimicrobials in veterinary medicine is the scientific and technically directed use of these compounds, which should form an integral part of good veterinary and animal husbandry practices.

All the relevant stakeholders, viz. the authorities, the veterinary pharmaceutical industry, veterinarians, pharmacists, pet owners and livestock keepers, must apply these principles.

Methods of disease prevention (e.g. vaccination and improvements in conditions of husbandry) must be considered when disease problems become evident, thus minimising the use of antimicrobial agents to compensate for deficient animal husbandry practices.

On-going disease and therapeutic monitoring must accompany the use of antimicrobials. Resistance surveillance and monitoring programmes must also be implemented.

3.2 General principles

1. Antimicrobials should be used under the supervision of a veterinarian within the context of a valid veterinarian-client-patient relationship.
2. Veterinarians should work with those responsible for the care of animals to encourage the judicious use of antimicrobials, regardless of the distribution system through which the antimicrobial was obtained.
3. Therapeutic antimicrobials should only be used when it is known or suspected that an infectious agent is present, which will be susceptible to therapy.
4. Regimens for therapeutic antimicrobial use should be optimised using current pharmacological information and principles.
5. Therapeutic antimicrobial treatment should be limited to ill or at risk animals, treating the fewest animals indicated.
6. Environmental contamination with antimicrobials is to be avoided, whenever possible.
7. Accurate records of treatment and outcome should be used to evaluate therapeutic regimens.
8. Instructions on labels should be carefully followed and due attention paid to species and disease indications and contra-indications, dosage regimens and storage instructions. Extra-label use of antimicrobials should be exceptional and always under the professional responsibility of a veterinarians.
9. Emphasis should be placed on the prevention of disease and alternative therapeutic options in order to minimise the incidence of disease and therefore the need for antimicrobial use.
10. Antimicrobials considered important in treating refractory infections in human or veterinary medicine should only be used in animals after careful consideration and adequate justification.

3.3 Principles for the containment of antimicrobial resistance in animals

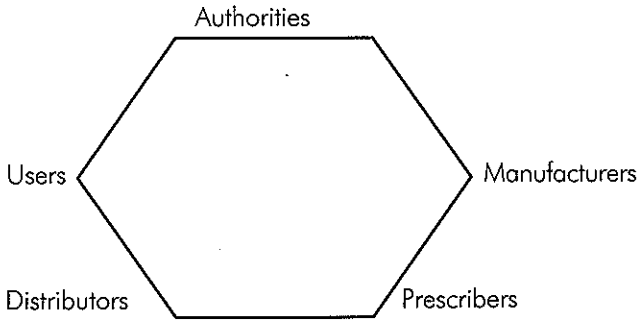
The WVA, Comisa, IAFF and WHO have jointly approved the fol-

lowing principles for the containment of antimicrobial resistance in animals:

- Technical guidelines for the prudent use of antimicrobials in animals must be available.
- Antimicrobial usage should be monitored appropriately.
- There should be a harmonised programme for the monitoring and surveillance of resistance to antimicrobial agents.
- An appropriate risk analysis methodology should be developed and applied to the use of antimicrobials.

4 RESPONSIBILITIES OF THE RELEVANT STAKEHOLDERS

All who are involved in the authorisation, manufacture, sale and supply, prescription and use of antimicrobials in livestock must act responsibly to limit the development of antimicrobial resistance.



4.1 Responsibilities of the relevant authorities

The regulatory authorities should institute appropriate authorisation procedures to ensure the safety, quality and efficacy of all antimicrobial products available for sale in their country. Evaluation should focus on each individual antimicrobial product and not be generalised to the class of antimicrobials to which the particular active principle belongs. Antimicrobial products should be reviewed periodically and a high degree of attention should be given to the question of anti-

microbial resistance both in the initial registration process and in subsequent reviews.

4.1.1 Implement an efficient registration procedure

Safety

- Risks to the animal, handler and consumer should be assessed.
- Safety evaluation should include consideration of the potential impact of the proposed use in food-producing animals on human health.

Quality

- Quality control procedures should be carried out in compliance with the provisions of good manufacturing practices.
- The specifications of analysis of antimicrobial agents used as active ingredients must comply with the provisions of approved monographs.
- The quality and concentration of antimicrobial agents in the marketed dosage forms must be maintained up to the expiry date under optimal storage conditions.
- The stability of antimicrobials when mixed with feeds or drinking water before being administered to animals must be determined.

Efficacy

- *Preclinical trials* must include pharmacodynamic and pharmacokinetic studies.

Pharmacodynamic studies should establish the activity of the antimicrobial agent towards the targeted bacteria. The mechanism of action must be considered, particularly with regard to possible mechanisms in terms of which resistance may develop. The following criteria should also be assessed:

- Whether the activity of the agent is time or concentration-dependent
- The minimum inhibitory concentration (MIC) and bactericidal concentration (MBC).
- The effects of changes in tissue pH, the presence of exudates and

differences in redox potential on the activity of the antimicrobial agent.

Pharmacokinetic studies must also be done to determine the bioavailability of the active ingredient using the intended route of administration. These studies should describe the distribution, metabolism and excretion of the antimicrobial in the treated animal and its concentration at the site of infection. Plasma concentrations are usually used for these studies; however, tissue concentrations or other biological fluids may be more appropriate, depending on the site of infection of the target pathogen. The time-concentration data in the plasma or site of infection should be compared to the target concentrations (i.e. MBC or MIC) and the pharmacokinetic data should support the selected dosing schedule.

The use of combinations of antimicrobial agents should be justified, taking into account both pharmacodynamics (synergistic or additive effects) and pharmacokinetics (maintenance of levels of associated antimicrobials).

- The ability of the antimicrobial agent to select for resistant bacteria *in vivo* and *in vitro* should also be assessed during preclinical trials. In certain cases, these trials should evaluate not only bacteria in the target animals, but also the impact of the antimicrobial use in food-borne/ commensal bacteria or certain indicator bacteria. Consideration should be given to the following:
- The concentration of the 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 that develop.
- 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).

Clinical trials

The final dose regimen should be based on pharmacokinetic/ pharmacodynamic data as well as on dose determination and dose confirmation studies conducted during the clinical trials.

The following criteria should be considered during the assessment of these trials:

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

The registration of new antimicrobial molecules, formulations etc., considered to have the potential to make important contributions to the control of resistance, should be expedited where possible.

4.1.2 Implement an appropriate scheduling and control system

An appropriate scheduling and control system should be implemented by which antimicrobials are supplied only through licensed/ authorised distribution systems. Antimicrobials in veterinary medicine should be prescribed by a veterinarian and delivered by an authorised public health professional. The antimicrobials must be administered to animals by a veterinarian or under his/her supervision.

All countries should make every effort to prevent the distribution and use of illegal and counterfeit products.

4.1.3 Supply sufficient and appropriate information

Sufficient and appropriate information necessary for the proper use of veterinary medicinal products containing antimicrobial agents must be supplied. This information must appear on the label and package insert of the product and consists of the following:

- Pharmacological properties
- Target animal species
- Therapeutic indications
- Dosage and administration route
- Withdrawal periods
- Incompatabilities
- Expiry date
- Particular precautions for animal and operator safety

- Particular precautions for the proper disposal of unused products

If dose ranges and/or different durations of treatment are suggested, guidance should be given on the approved product labelling, regarding the conditions that will minimise the development of resistance. The regulatory authority should play a significant role in specifying the terms of marketing authorisation. The conditions of use of an antimicrobial agent in veterinary medicine should be based on a safety evaluation, which takes into consideration the importance of the drug, or other antimicrobial agents belonging to the same therapeutic class, in human and/or veterinary medicine. Antimicrobials used to treat critical diseases in humans should only be used in animals when other therapies are unavailable or inappropriate.

4.1.4 Develop guidelines for the extra-label use of antimicrobial agents in veterinary medicine.

4.1.5 Conduct post-marketing surveillance
The regulatory authority should conduct both specific and non-specific post-marketing surveillance and monitoring programmes.

- There should be epidemiological surveillance of antimicrobial resistance, accompanied by a continuous survey of the amounts of antimicrobial agents used by veterinarians and other authorised users. Results of a risk analysis should be used to prioritise antimicrobials and animal bacteria for such surveillance. The methods used in such a programme should be harmonised as much as possible at an international level to expedite the process.
- Specific antimicrobial agents may be selected for surveillance, if this is justified by the safety evaluation that was carried out during the registration process. Such a specific surveillance programme would assess the impact of the use of the authorised antimicrobial agent on the selection of antimicrobial resistant bacteria in food-producing animals (target animal pathogens, food-borne pathogens and/or commensals).
- The conditions of use of antimicrobial agents in veterinary medicine should be modified in response to the results of post-marketing surveillance.

4.1.6 Establish acceptable daily intakes, minimum residue limits and withdrawal periods
An acceptable daily intake (ADI), and a maximum residue limit (MRL) for each animal derived food must be established. Withdrawal periods are also to be established for each veterinary medicinal product containing antimicrobial agents, which will make it possible to produce safe food in compliance with the MRLs. These withdrawal periods should take into account the pharmaceutical form, the target animal species, the dosage regimen, route of administration and duration of treatment.

4.1.7 Assess the impact of the proposed antimicrobial use on the environment.

4.1.8 Control advertising
The authorities must ensure that the advertising of antimicrobial agents complies with the granted marketing authorisation and is restricted to the authorised users in accordance with the scheduling status.

4.1.9 Training
The training of users (veterinarians and livestock keepers) should be encouraged. The regulatory authorities, professional associations, veterinary schools and research institutes may be involved in such training programmes. The programmes should focus on:

- Information on disease prevention and management strategies to decrease the use of antimicrobials
- The importance of proper diagnostic actions (bacteriological diagnosis and susceptibility testing)
- The ability of antimicrobials to select for resistant bacteria in food-producing animals that may cause animal and/or human health problems
- The need to use antimicrobial agents in animal husbandry in agreement with the provisions of the marketing authorisation and/or the veterinary prescription
- Relevant pharmacokinetic and pharmacokinetic information to enable the veterinarian to use antimicrobials prudently
- The need to observe the provisions of this code of prudent use

4.1.10 Research

Public and private research should be encouraged to:

- Improve the knowledge of the mechanism of action of antimicrobials.
- Improve knowledge about the mechanisms of emergence, selection and transfer of antimicrobial resistance genes in bacteria.
- Develop methods of applying risk analysis to the effect of antimicrobial resistance on public health.
- Develop methods of predicting, during the registration process, the impact of the proposed use of an antimicrobial agent on the rate and extent of resistance development.
- Develop alternative methods to control bacterial diseases (vaccines, probiotics, management and disease eradication programmes).

4.2 Responsibilities of the pharmaceutical industry

4.2.1 Comply with marketing authorisation requirements

A veterinary pharmaceutical company that wishes to apply for registration of an antimicrobial product must supply the requested information, which is needed to objectively establish the safety, efficacy and quality of the product, to the national regulatory authority. The quality of this information must be guaranteed on the basis that procedures, tests and trials were conducted in compliance with the provisions of good manufacturing, good laboratory and good clinical practices.

4.2.2 Market and export of veterinary medicines responsibly

Only registered veterinary medicinal products should be sold and supplied, and then only through licensed/ authorised distribution systems. All veterinary medicinal products that are exported should be approved for sale in the exporting country or should have received a certificate, assuring their quality, from the regulatory authorities.

4.2.3 Comply with Good Manufacturing Practices

4.2.4 Supply information

- Product information must be disseminated in compliance with the provisions of the granted authorisation and should only reach the authorised professionals for whom it is intended.

- Veterinary pharmaceutical companies should participate in the training of the users of their products.
- Veterinary pharmaceutical companies must provide information to the regulatory authorities about the quantity of antimicrobial agents marketed.

4.3 Responsibilities of the pharmacist

Pharmacists distributing veterinary antimicrobials must comply with good dispensing practice. Antimicrobials are to be supplied in accordance with scheduling requirements, and products that have not been exempted from scheduling may only be supplied on the prescription of a veterinarian. Accurate information must be conveyed to the user and all products should be appropriately labelled.

4.4 Responsibilities of the veterinarian

Veterinarians should only prescribe antimicrobials to *bona fide* clients for 'animals under his/her care'. He/she must comply with scheduling requirements when prescribing products.

Antimicrobial agents should only be used when necessary and then selected rationally and used appropriately. Appropriate records and stock control should be kept.

Consideration should be given to potential consequences of resistance to the specific substance in question. Selection of antimicrobials that are used for animals or humans in special, critical situations where few or no other antimicrobials are available should be carefully justified. Fluoroquinolones, dichloroacetic acid derivatives, newer generation macrolides and cephalosporins should only be used therapeutically and not for routine prophylaxis or growth promotion.

The use of antimicrobials can only be justified for the prevention of disease where it can be shown that a particular disease is present on the premises or is likely to become so, or where other diseases or treatment modalities may compromise immunocompetence. In such circumstances it should be shown that strategic use of antimicrobials would prevent clinical outbreaks of that disease.

Veterinarians should remain abreast of new scientific developments through participating in continuing education programmes.

4.5 Responsibilities of the users

- Isolate sick animals to decrease the transfer of resistant bacteria.
- Use antimicrobial agents only on veterinary prescription and according to the provisions of the prescription.
- Store veterinary products that contain antimicrobials correctly.
- Practice good hygiene when there is contact between people (veterinarians, breeders, owners, children) and treated animals.
- Comply with the recommended withdrawal periods.
- Dispose of surplus antimicrobials in a manner that will not contaminate the environment. Partially used products should not be kept for later use, unless this is authorised by a veterinarian.
- Alternative strategies should be developed, in consultation with a veterinarian, to control or prevent recurrent disease problems.
- Livestock owners should maintain adequate records:
  - Date of administration of antimicrobial agent
  - Identification of the animal or group of animals to which the antimicrobial agent was administered
  - Diagnosis/ clinical condition treated
  - Identity and quantity of the antimicrobial agent administered
  - Name and address of the supplier of the antimicrobial
  - Batch number
  - Withdrawal periods
  - Effectiveness of therapy
- Results of laboratory tests

5 MONITORING OF ANTIMICROBIAL USAGE

The monitoring of the amount of antimicrobial agents used in veterinary medicine is essential for risk analysis and planning. It is also helpful in interpreting resistance surveillance data and evaluating the effectiveness of prudent use efforts.

A number of different types of data can be collected, depending on the objectives of the monitoring programme and the availability of the required data.

Data that can be collected at three levels:

- Regulatory authorities
- Veterinary pharmaceutical industry
- Prescribers, distributors and users of veterinary medicinal products containing antimicrobials

In addition to data on the total amount of antimicrobial products sold (according to the different classes), other useful data can include the species for which the products are prescribed, the type of farming systems and enterprises involved, and the regional and seasonal variations in usage.

6 RESISTANCE MONITORING AND SURVEILLANCE

Resistance monitoring and surveillance has become a necessary part of the responsible and prudent use of antimicrobials in veterinary medicine. It initially arose from the need to give guidance to practitioners on appropriate therapy, but more recently these programmes have been designed to extend knowledge about antimicrobial resistance in food-borne pathogens. These programmes include the evaluation of local, regional and national trends. The data generated will eventually play a role in the development of policies for the containment of antimicrobial resistant pathogens from animals and their immediate environment.

Surveillance is the continuous investigation of a given population to detect the occurrence of antimicrobial resistance and to control it. This may be done by testing a part of the population.

Monitoring constitutes on-going programmes directed at the detection of changes in the prevalence of antimicrobial resistance in a given population and in its environment.

The objectives of implementing a resistance monitoring and surveillance programme are to:

- Detect the emergence of resistance
- Determine the prevalence or trends of prevalence to a particular drug or class

- Determine prevalence and/or trends of reduced specific drug susceptibility in a defined population
- Provide data for risk analysis regarding human and animal health
- Provide a basis for policy recommendations for animal and public health
- Provide information for prescribing practitioners
- Generate data that may guide the design of further studies
- Identify the need for potential interventions and assess impact

Surveillance and monitoring programmes should be harmonised nationally and internationally.

The following factors should be considered regarding the harmonisation of these programmes:

- Animal species/ categories (including age) to be sampled
- Sampling strategy to be employed
- Sample specimens to be collected
- Bacterial species to be used in susceptibility testing
- Standardised susceptibility testing
- Quality control and assurance procedures
- Type of quantitative data to be reported
- Data base design and recording of results
- Reporting and analysis of results

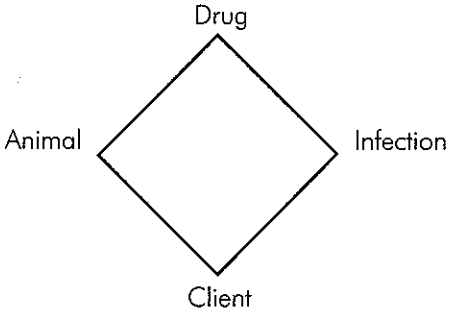
Laboratory methodology should also be standardised and harmonised:

- Standardise antimicrobial susceptibility testing method
- Harmonise susceptibility data
- All data must be reproducible and reported quantitatively
- Establish national or regional designated laboratories
- Conduct work under internal quality assurance
- Accredit laboratories
- Use of specific bacterial/quality control systems
- Co-ordination with appropriate international organisation or agencies

7 GENERAL PRINCIPLES OF THE RATIONAL SELECTION AND USE OF ANTIMICROBIALS

The rational use of antimicrobial agents entails selection of the proper drug to be administered according to a dosage regimen appropriate to the patient, after due consideration of the potential benefits and risks of that therapy.

The following four factors should be considered:



7.1 Drug factors

7.1.1 Drug formulation

Drugs are generally administered in prepared dosage forms (e.g. parenteral preparations for injection and tablets, capsules or suspensions for oral administration). Drug formulations should be administered only by the route(s) for which the manufacturer developed the formulation.

Different formulations do not provide identical concentrations in tissue. As a rule, the slower a drug is absorbed, the lower the peak plasma concentrations will be.

- For infections with organisms that require high minimum inhibitory concentrations, use formulations that will provide the highest concentrations in the target tissue (e.g. sodium ampicillin attains higher tissue concentrations than ampicillin trihydrate).
- For acute, life-threatening infections, use the route of administration that will result in the highest peak plasma concentrations being attained as quickly as possible (e.g. intravenous administration of penicillin).

When choosing a dosage form and route of administration, convenience should be considered in order to promote client compliance.

7.1.2 Antimicrobial action

Antimicrobial action includes the mechanism of action, antimicrobial effect and spectrum of activity.

The ideal antimicrobial agent is the one to which the causative organism is most sensitive and **also** one that achieves effective concentrations at the site of infection without damaging the host.

The antimicrobial sensitivity of gram positive bacteria is generally predictable. This is in contrast to gram negative bacteria that readily acquire transferable resistance. Published tables of susceptibility for groups of antimicrobial agents are useful in determining the first choice of agent to treat a particular infection. However, veterinarians should have access to laboratories where antimicrobial susceptibility can be determined reliably. The sensitivity of the microorganism can be determined by minimum inhibitory concentration (MIC) data or the results of disc diffusion tests.

The first line of choice should be based on products approved for the species and for the indication concerned. When no suitable product is licensed for a specific condition or species, the choice of an alternative product should be based, whenever possible, on the results of well performed field trials and a proven efficacy for the condition or species concerned. Indiscriminate off-label use should be avoided.

The mechanism of action of the drug will influence the rate of drug effect, its effect on the microbial organism, and its potential toxic effects on the host as well as its activity at the biophase. Drugs with similar mechanisms of action should not be alternated when microbial insensitivity is observed. Consideration should be given to the fact that some drugs such as penicillin, aminoglycosides and fluoroquinolones have a post-antibiotic effect. Activity of these drugs continues to exist for a period after blood concentrations fall below effective concentrations once treatment has ceased.

Bactericidal drugs are needed in the following conditions:

1. Where host defences are impaired
2. Where serious infections such as meningitis, endocarditis and osteomyelitis exist
3. In immunodeficient or immunosuppressed animals.

In other cases bacteriostatic antimicrobials should be equally useful.

Where appropriate, the use of narrow-spectrum antimicrobial agents is preferable to broad-spectrum agents because the narrow spectrum interferes less with the normal microbial flora of the host and is less likely to lead to broad antimicrobial resistance.

7.1.3 Pharmacokinetic considerations

The choice of the correct antimicrobial must consider pharmacokinetic parameters such as bioavailability, tissue distribution and biological half-life to ensure that the selected therapeutic agent reaches the site of infection at sufficient concentration and/or duration.

7.1.4 Dosage

Attention should be paid to the dose, dosage interval, duration of treatment, recommended route of administration and withdrawal periods.

All medicinal products should be used according to the conditions of the marketing authorisation, which are reflected on the label and package insert of the product. However, prescribing veterinarians have the right to adapt these if considered necessary, using sound clinical judgement. The use of drugs in ways that are not in accordance with the marketing authorisation is termed 'extra-label' use. Veterinarians should be aware that under circumstances of extra-label use, they take full responsibility for such use. Extra-label use must therefore at all times be defendable on the basis of the risk-benefit ratio. Veterinarians must inform clients if a product is being used extra-labelly. The veterinarian should obtain written consent from the client to use the product.

Dosages may have to be modified in neonates and in animals with

impaired liver or kidney function.

Dose:

To some extent, the susceptibility of the organism and the site of the infection determine the dose given. Thus, for highly susceptible bacteria in nonspecialised sites, low doses would be adequate. However, for less susceptible bacteria, particularly in sites where drugs do not penetrate well, doses should be higher.

The factor that most frequently limits the dose given is host toxicity. Therefore, the upper dose limit should not be exceeded, because this limit is often determined by toxicity. Some antimicrobial agents (e.g. penicillin G) have an optimal concentration for their antibacterial action. Since penicillin G is a virtually nontoxic drug, its dose is limited by its antibacterial action. This is in contrast to the more toxic antimicrobial agents such as the aminoglycosides

Dosage interval:

The activity of antimicrobial drugs may be concentration or time dependent. For concentration dependent antimicrobials, the bactericidal effect is dependent on the attainment of adequate peak concentrations, after which concentrations can be allowed to fall below the Minimum Inhibitory Concentration. In this way, toxicity can also be minimised by preventing the accumulation of the drug in tissue (e.g. gentamicin). For time dependent antimicrobials, it is essential that concentrations be maintained above the Minimum Inhibitory Concentration for the entire duration of the treatment (e.g. penicillins).

The fact that an antimicrobial is concentration dependent or time dependent must be considered when determining the dosage intervals for that drug.

Duration of treatment:

Antimicrobials used for therapy should be used for as long as needed, over as short a dosage period as possible. Insufficient duration of administration can lead to recrudescence of the infection and the increased likelihood of selecting microorganisms with reduced sensitivity.

The duration of treatment must be limited to only that required for

therapeutic effect. This will minimise the exposure of the bacterial population to the antimicrobial. The adverse effects on the surviving commensal microflora are minimised and the medical impact of the remaining zoonotic organisms is minimised/reduced. Generally, it should be clear within 2 days whether or not therapy is clinically effective. If no response is seen by that time, both the diagnosis and treatment should be reconsidered.

Theoretically, antimicrobial use should be stopped as soon as the animal's own host defence system can control the infection itself. Practically, treatment should be continued for at least 2 days after clinical and microbiologic resolution of infection, and longer for certain types of infections, particularly those in which cell-mediated immunity is a factor.

Route of administration:

The route of administration will determine the rate and extent of absorption as well as the peak concentration of the active ingredient attained at the site of infection.

Parenteral therapy should always be used in the treatment of acute infections. In mild to moderate infections, oral therapy is more convenient in dogs and cats, and is therefore preferred for antimicrobial agents that show reliable absorption from the gastro-intestinal tract. The oral route is also preferred for long-term administration of those preparations that cause tissue irritation at the site of injection. The oral route is not considered to be desirable in horses and ruminants due to the influence on the gastro-intestinal microflora.

Aminoglycosides, used for the treatment of systemic gram-negative infections, must always be administered parenterally (IM or SC) as these water-soluble drugs are not absorbed from the gastro-intestinal tract.

It should also be remembered that the oral route increases the access of antimicrobial agents to the complex gastrointestinal flora, which may enhance the selection for and transfer of resistance genes. Antimicrobial drugs that are administered parenterally but are excreted to a large extent through the bile may similarly select for resistance.

Withdrawal period:
Withdrawal periods may limit the selection and use of antimicrobial drugs in food producing animals. In food-producing animals, the recommended withdrawal periods should always be observed to prevent residues of antimicrobial agents occurring in tissues, eggs or milk. With extra-label use, an extended withdrawal period should ensure that there are no tissue residues.

7.1.5 Combined or concurrent use
The indiscriminate use of antibiotic combinations should be avoided because of the potential for increased toxicity, pharmacological antagonism and the selection of resistant organisms. However, the use of combination therapy may be necessary in certain circumstances (e.g. mixed infections not susceptible to single agents, in order to achieve a synergistic effect, **so as** to use toxic drugs in lower doses, in order to institute therapy on an empirical basis in life threatening situations or so as to prevent the emergence of resistant strains of organisms in chronic infection).

The use of multiple antimicrobials in order to provide broader coverage may be justified when failure to initiate effective antibiotic therapy will significantly increase mortality or morbidity or in seriously ill patients when the identity of an infecting organism is not apparent.

When instituting combined therapy, the mechanism of action of the different antimicrobial drugs should be considered. Agents should act at different sites to avoid competing for the same enzymes and substrates (e.g. a combination of lincomycin and erythromycin would both act at the 50s ribosome level).

Generally, bacteriostatic and bacteriocidal drugs should not be used together. There are, however, exceptions.

The following are examples of antimicrobials that have demonstrated evidence of synergism:

- Penicillin and streptomycin in endocarditis caused by *E.coli*.
- Polymyxin and sulphonamides in urinary tract infections caused by certain strains of *Proteus*.

- Carbenicillin and gentamicin for gentamicin resistant *Pseudomonas* infections
- Sulphonamides and trimethoprim

7.1.6 Adverse drug reactions
Adverse reactions and/or side-effects to antimicrobial agents may be directly dose related or may occur at normal therapeutic dosages. The reactions may present acutely or result in chronic effects due to continued long term use.
The use of antimicrobial drugs must at all times be defendable on the basis of risk-benefit assessment.

Direct organ system toxicity:
Antimicrobial therapy of disease is based on the principle that selective toxicity of the drug for the causative microorganism will occur before any toxic effect on the host does.

However, the selective toxicity of antimicrobials is variable, with some agents (e.g. beta-lactams) that are generally very safe and others (e.g. aminoglycosides) that are dangerously toxic.

- Consider that antimicrobials may exacerbate the pathophysiological effects of the disease condition of a patient due to their adverse effects (e.g. aminoglycosides with kidney damage and macrolides with hepatic damage).
- Antimicrobials with a low safety margin should not be administered to animals with disease of the organs responsible for the elimination of that agent.

Teratogenicity, mutagenicity and carcinogenicity:
It must be remembered when using antimicrobials in pregnant animals that most drugs cross the placental barrier and can produce toxicities in the offspring without affecting the dam. Beta-lactams, macrolides and lincosamides are considered to be safe in pregnancy.

Interactions with other drugs:
The concurrent administration of antimicrobial agents together with other drugs may lead to changes in drug metabolism, competition for receptor sites and competition for excretory pathways.

Effects on the intestinal flora:
The use of antimicrobial agents may interfere with the protective effect of the normal host microflora or disturb the metabolic function of the microbial flora in the digestive tract of herbivores. Consideration should be given to these effects, particularly with orally administered agents and the long term use of broad spectrum antimicrobials.

Hypersensitivity reactions:
Although hypersensitivity reactions are rare in veterinary medicine, do not administer a particular type of antimicrobial to patients that have a history of hypersensitivity to that substance.

Immunosuppresion:
Some antimicrobial drugs have been observed to reduce phagocytosis, chemiluminescence and chemotactic activity *in vitro*. The clinical significance of these observations is uncertain. There may be some application in immunosuppressed or neutropaenic patients. Also, it may be inappropriate to immunise animals with nonadjuvanated, killed vaccines while concurrently administering an antimicrobial that inhibits protein synthesis.

Tissue reactions:
A number of antimicrobial drugs and formulations may cause tissue reactions and necrosis at the site of injection.

7.2 Microbial infection

7.2.1 Documentation of infection

Therapeutic antimicrobials should only be used when it is known or suspected that an infectious agent is present which will be susceptible to therapy. The establishment of an etiological diagnosis must be based on adequate diagnostic procedures.

The most common error in antibacterial therapy is its use in patients that have viral, mycotic, neoplastic or parasitic diseases.

7.2.2 Sensitivity of the infection

Ideally, the choice of antimicrobial for the treatment of infectious disease should be based on the identification of the causative agent and antimicrobial sensitivity tests wherever possible. Identification and sensitivity testing is particularly important in the following cases:

- Situations where disease spread is likely and in animals where treatment failure has occurred.
- Where the pathogen is of a type, which is often resistant to antimicrobial drugs (*Staph.* spp. and most of the family *Enterobacteriaceae.*)
- Where the infection was unresponsive to initial therapy or is of a chronic recurring nature.
- Where the most effective antimicrobial drug is needed for the treatment of life-threatening infections or immune suppressed patients.
- Where the most effective antimicrobial drug cannot be used due to potential toxic- or side-effects (e.g. nephrotoxicitiy of gentamicin in a patient with pre-existing renal disease).

In disease outbreaks involving high mortality or where there are signs of rapid spread of disease among contact animals, treatment may have to be started on the basis of clinical diagnosis.

- Samples must be collected for bacterial culture before the initiation of antimicrobial therapy and must be handled in such a manner that bacteria cell death, bacterial overgrowth and contamination are avoided.
- While therapy may need to be initiated before results of diagnostic or antimicrobial sensitivity tests are known, it will need to be reassessed as test results become available.

It is not always necessary to culture samples from all patients with infectious diseases in order to identify the organisms involved.

- A clinical diagnosis can be based on knowledge of the usual invaders of a given system, of what was previously effective in similar types of problems and on any knowledge of previous antimicrobial efficacy on the premises.
- A presumptive microbiological diagnosis can also be made on the basis of direct microscopical examination of stained material.

It is important to remember that antimicrobial sensitivity testing can only give an indication of the *in vitro* response of the drug against the

causative organisms. Results may also be misleading for several other reasons, including failure to isolate the causative organism (e.g. anaerobes), misinterpretation of the significance of normal flora, and incorrect handling of samples and swabs in transit to the laboratory.

Clear therapeutic objectives must be set before treatment is begun and the efficacy of all disease treatments should be monitored. Antimicrobial sensitivity trends should be monitored over time, and such monitoring used to guide clinical judgement on antimicrobial usage.

Should there be a recurrence of disease following successful treatment or control of an outbreak, it may need to be investigated more thoroughly, depending on the situation, to ascertain the reason for recurrence and the most suitable therapy to be used.

7.2.3 Growth stage of the infection
Most drugs are effective in the early log growth phase of bacterial infection. This applies particularly for bacteriostatic drugs but also penicillin.

- Antibacterial drugs should be used as early as possible in the development of the disease.
- Large doses given early in the infection when bacterial numbers are still low will improve the action of antimicrobial drugs.

7.2.4 Locality of the infection
The location of the infection can have a major influence on the drug concentration achieved there.

- Consider that some sites (e.g. the central nervous system) may be protected by barriers to drug penetration. The ability of an administered antimicrobial to penetrate these barriers will depend on its lipid solubility, molecular size and pKa.
- Remember that inflammation may enhance the penetration of antimicrobial drugs into tissues that they would normally enter in restricted amounts. This increases the choice of antimicrobials for the treatment of infections at these sites.
- Consider that the pH in certain parts of the body may favour drug accumulation (e.g. mammary gland, urinary tract). This can be used to attain higher concentrations of antimicrobials within these

tissues.

7.2.5 Micro-environment at the site of the infection
The micro environment at the site of infection must be favourable for drug action, e.g. sulphonamides are rendered ineffective when cellular debris and blood products are present; oxygen is required for the bacterial uptake of aminoglycosides, making them ineffective against susceptible bacteria in anaerobic conditions; penicillins and cephalosporins may not kill bacteria in environments that are iso-osmotic to the internal environment of the bacteria.

7.2 Animal factors

Animal factors that should be considered are:

- Type of animal
- Age of animal
- Condition of animal
- Sex
- Disease condition
- Type of husbandry
- Feeding of animals

7.3 Client factors

Prudent use of antimicrobials is a partnership between the veterinarian and client and must involve agreement on treatment policy and veterinary involvement in on-going disease conditions.

The level of involvement of the veterinarian will depend on the level of training and experience of the client, as well as on the level of responsibility of the animal caretaker.

- Veterinarians should work with those responsible for the care of animals to use antimicrobials judiciously, regardless of the distribution system through which the antimicrobial was obtained.
- A prescription for antimicrobial agents must precisely indicate the treatment regime, the dose and dosage interval, the duration of the treatment, the withdrawal period and the amount of drug to be delivered, as depending on the dosage regimen and the number of animals to be treated.
- Quantities of antimicrobials left with the animal owner should correctly reflect the needs of the animals in order to avoid

oversupply.

- Veterinarians must comply with the legal requirements regarding dispensing and labeling of antimicrobials.
- Written protocols or policies should be agreed upon and documented for treatment of all endemic conditions on the farm or other livestock rearing or production premises. These protocols should be regularly reviewed and updated.
- Codes of good practices, Quality Assurance Programmes, Herd Health Surveillance Programmes and education programmes should promote the responsible and prudent use of antimicrobials.

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