CHAPTER 6.9.

RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN VETERINARY MEDICINE

Article 6.9.1.

Purpose

These recommendations provide guidance for the responsible and prudent use of antimicrobial agents in veterinary medicine, with the aim of protecting both animal and human health. The Competent Authorities responsible for the registration and control of all groups involved in the production, distribution and use of veterinary antimicrobials have specific obligations.

Prudent use is principally determined by the outcome of the marketing authorisation procedure and by the implementation of specifications when antimicrobials are administered to animals.

Article 6.9.2.

Objectives of prudent use

Prudent use includes a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals to:

1. 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;

2. comply with the ethical obligation and economic need to keep animals in good health;

3. prevent, or reduce, as far as possible, the transfer of micro-organisms (with their resistance determinants) within animal populations;

4. maintain the efficacy of antimicrobial agents used in food-producing animals;

5. prevent or reduce the transfer of resistant micro-organisms or resistance determinants from animals to humans;

6. maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of the antimicrobials;

7. prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);

8. protect consumer health by ensuring the safety of food of animal origin with respect to residues of antimicrobial drugs, and the ability to transfer antimicrobial drug resistant micro-organisms to humans.
Responsibilities of the regulatory authorities

1. Marketing authorisation

The national regulatory authorities are responsible for granting marketing authorisation. This should be done in accordance with the provisions of the Terrestrial Code. They have a significant role in specifying the terms of this authorisation and in providing the appropriate information to the veterinarian.

2. Submission of data for the granting of the marketing authorisation

The pharmaceutical industry has to submit the data requested for the granting of the marketing authorisation. The marketing authorisation is granted only if the criteria of safety, quality and efficacy are met. An assessment of the potential risks and benefits to both animals and humans resulting from the use of antimicrobial agents in food-producing animals should be carried out. The evaluation should focus on each individual antimicrobial product and the findings not be generalised to the class of antimicrobials to which the particular active principle belongs. Guidance on usage should be provided for all dose ranges or different durations of treatment that are proposed.

3. Market approval

Regulatory authorities should attempt to expedite the market approval process of a new antimicrobial in order to address a specific need for the treatment of disease.

4. Registration procedures

Countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicinal products (VMPs), and whose supply principally depends on imports from foreign countries, should undertake the following measures:

a) check the efficacy of administrative controls on the import of these VMPs;
b) check the validity of the registration procedures of the exporting and manufacturing country as appropriate;
c) develop the necessary technical co-operation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

Regulatory authorities of importing countries should request the pharmaceutical industry to provide quality certificates prepared by the Competent Authority of the exporting and manufacturing country as appropriate. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of unlicensed and counterfeit bulk active pharmaceutical ingredients and products.

5. Quality control of antimicrobial agents

Quality controls should be performed:

a) in compliance with the provisions of good manufacturing practices;
b) to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs;
c) to ensure that the quality and concentration (stability) of antimicrobial agents in the marketed dosage form(s) are maintained until the expiry date, established under the recommended storage conditions;
d) to ensure the stability of antimicrobials when mixed with feed or drinking water;
e) to ensure that all antimicrobials are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

6. Assessment of therapeutic efficacy
   a) Preclinical trials
      i) Preclinical trials should:
         - establish the range of activity of antimicrobial agents on both pathogens and non-pathogens (commensals);
         - assess the ability of the antimicrobial agent to select for resistance in vitro and in vivo, taking into consideration pre-existing resistant strains;
         - establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit the selection of antimicrobial resistance. (Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal.)
      ii) The activity of antimicrobial agents towards the targeted micro-organism should be established by pharmacodynamics. The following criteria should be taken into account:
         - spectrum of activity and mode of action;
         - minimum inhibitory and bactericidal concentrations;
         - time- or concentration-dependent activity or co-dependency;
         - activity at the site of infection.
      iii) The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:
         - 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 that may lead to the inactivation of antimicrobials;
         - excretion routes.
         Use of combinations of antimicrobial agents should be scientifically supported.
   b) Clinical trials
      Clinical trials should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:
      i) diversity of the clinical cases encountered when performing multi-centre trials;
      ii) compliance of protocols with good clinical practice, such as Veterinary International Cooperation on Harmonisation (VICH) guidelines;
      iii) eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;
      iv) parameters for qualitatively and quantitatively assessing the efficacy of the treatment.
7. Assessment of the potential of antimicrobials to select for resistance

Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistance. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered:

a) the concentration of active compound in the gut of the animal (where the majority of potential food-borne pathogens reside) at the defined dosage level;

b) the route and level of human exposure to food-borne or other resistant organisms;

c) the degree of cross-resistance within the class of antimicrobials and between classes of antimicrobials;

d) the pre-existing level of resistance in the pathogens of human health concern (baseline determination) in both animals and humans.

8. Establishment of acceptable daily intake, maximum residue level and withdrawal periods for antimicrobial compounds

a) When setting the acceptable daily intake (ADI) and MRL for an antimicrobial substance, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.

b) The establishment of an ADI for each antimicrobial agent, and an MRL for each animal-derived food, should be undertaken.

c) For each VMP containing antimicrobial agents, withdrawal periods should be established in order to produce food in compliance with the MRL, taking into account:
   i) the MRL established for the antimicrobial agent under consideration;
   ii) the composition of the product and the pharmaceutical form;
   iii) the target animal species;
   iv) the dosage regimen and the duration of treatment;
   v) the route of administration.

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

9. Protection of the environment

An assessment of the impact of the proposed antimicrobial use on the environment should be conducted. Efforts should be made to ensure that the environmental impact of antimicrobial use is restricted to a minimum.

10. Establishment of a summary of product characteristics for each veterinary antimicrobial product

The summary of product characteristics contains the information necessary for the appropriate use of veterinary antimicrobial product (VAP) and constitutes the official reference for their labelling and package insert. This summary should contain the following items:

a) active ingredient and class;

b) pharmacological properties;

c) any potential adverse effects;

d) target animal species and age or production category;
e) therapeutic indications;
f) target micro-organisms;
g) dosage and administration route;
h) withdrawal periods;
i) incompatibilities;
j) shelf-life;
k) operator safety;
l) particular precautions before use;
m) particular precautions for the proper disposal of un-used or expired products;
n) information on conditions of use relevant to the potential for selection of resistance.

11. Post-marketing antimicrobial surveillance

The information collected through existing pharmacovigilance programmes, including lack of efficacy, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this, the following should be considered:

a) General epidemiological surveillance

The surveillance of animal micro-organisms resistant to antimicrobial agents is essential. The relevant authorities should implement a programme according to the Terrestrial Code.

b) Specific surveillance

Specific surveillance to assess the impact of the use of a specific antimicrobial may be implemented after the granting of the marketing authorisation. The surveillance programme should evaluate not only resistance development in target animal pathogens, but also in food-borne pathogens and/or commensals. Such a surveillance will also contribute to general epidemiological surveillance of antimicrobial resistance.

12. Supply and administration of the antimicrobial agents used in veterinary medicine

The relevant authorities should ensure that all the antimicrobial agents used in animals are:

a) prescribed by a veterinarian or other authorised person;
b) supplied only through licensed/authorised distribution systems;
c) administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons.

The relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

13. Control of advertising

All advertising of antimicrobials should be controlled by a code of advertising standards, and the relevant authorities must ensure that the advertising of antimicrobial products:

a) complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;
b) is restricted to authorised professionals, according to national legislation in each country.
14. **Training of antimicrobial users**

The training of users of antimicrobials should involve all the relevant organisations, such as regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food-animal owners. This training should focus on:

a) information on disease prevention and management strategies;

b) the ability of antimicrobials to select for resistance in food-producing animals;

c) the need to observe responsible use recommendations for the use of antimicrobial agents in animal husbandry in agreement with the provisions of the marketing authorisations.

15. **Research**

The relevant authorities should encourage public- and industry-funded research.

**Article 6.9.4.**

**Responsibilities of the veterinary pharmaceutical industry**

1. **Marketing authorisation of VAPs**

   The veterinary pharmaceutical industry has responsibilities to:

   a) supply all the information requested by the national regulatory authorities;

   b) guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices;

   c) implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance.

2. **Marketing and export of VAPs**

   For the marketing and export of VAPs:

   a) only licensed and officially approved VAPs should be sold and supplied, and then only through licensed/authorised distribution systems;

   b) the pharmaceutical industry should provide quality certificates prepared by the Competent Authority of the exporting and/or manufacturing countries to the importing country;

   c) the national regulatory authority should be provided with the information necessary to evaluate the amount of antimicrobial agents marketed.

3. **Advertising**

   The veterinary pharmaceutical industry should:

   a) disseminate information in compliance with the provisions of the granted authorisation;

   b) ensure that the advertising of antimicrobials directly to the food animal producer is discouraged.

4. **Training**

   The veterinary pharmaceutical industry should participate in training programmes as defined in point 14 of Article 6.9.3.
5. **Research**

The veterinary pharmaceutical industry should contribute to research as defined in point 15 of Article 6.9.3.

**Article 6.9.5.**

**Responsibilities of wholesale and retail distributors**

1. Retailers distributing VAPs should only do so on the prescription of a veterinarian or other suitably trained person authorised in accordance with the national legislation, and all products should be appropriately labelled.

2. The recommendations on the responsible use of antimicrobials should be reinforced by retail distributors who should keep detailed records of:
   a) date of supply;
   b) name of prescriber;
   c) name of user;
   d) name of product;
   e) batch number;
   f) quantity supplied.

3. Distributors should also be involved in training programmes on the responsible use of antimicrobials, as defined in point 14 of Article 6.9.3.

**Article 6.9.6.**

**Responsibilities of veterinarians**

The concern of the veterinarian is to promote public health and animal health and welfare. The veterinarian’s responsibilities include preventing, identifying and treating animal diseases. The promotion of sound animal husbandry methods, hygiene procedures and vaccination strategies (good farming practice) can help to minimise the need for antimicrobial use in food-producing animals.

Veterinarians should only prescribe antimicrobials for animals under their care.

1. **Use of antimicrobial agents**

   The responsibilities of veterinarians are to carry out a proper clinical examination of the animal(s) and then:
   a) only prescribe antimicrobials when necessary;
   b) make an appropriate choice of the antimicrobial based on experience of the efficacy of treatment.

2. **Choosing an antimicrobial agent**

   a) The expected efficacy of the treatment is based on:
      i) the clinical experience of the veterinarian;
      ii) the activity towards the pathogens involved;
iii) the appropriate route of administration;

iv) known pharmacokinetics/tissue distribution to ensure that the selected therapeutic agent is active at the site of infection;

v) the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogens involved.

Should a first-line antimicrobial treatment fail or should the disease recur, a second line treatment should ideally be based on the results of diagnostic tests.

To minimise the likelihood of antimicrobial resistance developing, it is recommended that antimicrobials be targeted to pathogens likely to be the cause of infection.

On certain occasions, a group of animals that may have been exposed to pathogens 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.

b) Use of combinations of antimicrobials should be scientifically supported. Combinations of antimicrobials may be used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

3. Appropriate use of the antimicrobial chosen

A prescription for antimicrobial agents should indicate precisely the treatment regime, the dose, the treatment 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.

The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used. It is the veterinarian’s responsibility to define the conditions of responsible use in such a case including the therapeutic regimen, the route of administration, and the duration of the treatment.

4. Recording

Records on veterinary antimicrobial drugs should be kept in conformity with the national legislation. Information records should include the following:

a) quantities of medication used;

b) a list of all medicines supplied to each food-producing animal holding;

c) a list of medicine withdrawal period;

d) a record of antimicrobial susceptibilities;

e) comments concerning the response of animals to medication;

f) 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.

Veterinarians should also periodically review farm records on the use of VAPs to ensure compliance with their directions and use these records to evaluate the efficacy of treatment regimens.

5. Labelling

All medicines supplied by a veterinarian should be labelled according to the national legislation.
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6. **Training**

Veterinary professional organisations should participate in the training programmes as defined in point 14 of Article 6.9.3. It is recommended that veterinary professional organisations develop for their members species-specific clinical practice recommendations on the responsible use of VAPs.

**Article 6.9.7.**

**Responsibilities of food-animal producers**

1. Food-animal producers with the assistance of a veterinarian are responsible for implementing health and welfare programmes on their farms (good farming practice) in order to promote animal health and food safety.

2. Food-animal producers should:
   a) draw up a health plan with the attending veterinarian that outlines preventative measures (feedlot health plans, mastitis control plans, endo- and ectoparasite control and vaccination programmes, etc.);
   b) use antimicrobial agents only on prescription, and according to the provisions of the prescription;
   c) use antimicrobial agents in the species, for the uses and at the dosages 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;
   d) isolate sick animals, when appropriate, to avoid the transfer of pathogens; dispose of dead or dying animals promptly under conditions approved by the relevant authorities;
   e) comply with the storage conditions of antimicrobials in the rearing unit, according to the provisions of the leaflet and package insert;
   f) address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated;
   g) comply with the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;
   h) dispose of surplus antimicrobials under safe conditions for the environment; 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;
   i) maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the veterinarian responsible for treating the animals;
   j) keep adequate records of all medicines used, including the following:
      i) name of the product/active substance and batch number;
      ii) name of prescriber and/or the supplier;
      iii) date of administration;
      iv) identification of the animal or group of animals to which the antimicrobial agent was administered;
      v) clinical conditions treated;
      vi) dosage;
vii) withdrawal periods;
viii) result of laboratory tests;
ix) effectiveness of therapy;
k) inform the responsible veterinarian of recurrent disease problems.