

TERRESTRIAL ANIMAL HEALTH STANDARDS COMMISSION
SEPTEMBER 2011 REPORT

CHAPTER 6.9.

**RESPONSIBLE AND PRUDENT USE OF
ANTIMICROBIAL AGENTS
IN VETERINARY MEDICINE**

Article 6.9.1.

Purpose

This document ~~These recommendations~~ provides guidance for the responsible and prudent use of *antimicrobial agents* in veterinary medicine, with the aim of protecting both animal and human health. It defines the respective responsibilities of the *Competent Authorities* and stakeholders involved in the authorisation, production, control, distribution and use of veterinary medicinal products (VMP) containing antimicrobial agent(s) such as the national regulatory authorities, the veterinary pharmaceutical industry, veterinarians, distributors and food animal producers. The *Competent Authorities* responsible for the registration and control of all groups involved in the authorisation production, distribution and use of veterinary antimicrobials have specific obligations.

Responsible and Prudent use is principally determined by the outcome of the specifications detailed in the marketing authorisation procedure and by their implementation of specifications when antimicrobials agents are administered to *animals*.

Responsible and prudent use activities need to involve all stakeholders.

A coordination of these activities at the national or regional level is recommended and may support the implementation of targeted actions by the stakeholders involved and enable clear and transparent communications.

Article 6.9.2.

Objectives of responsible and prudent use

Responsible and Prudent use includes a set of practical measures and recommendations intended to prevent and/or reduce improve animal health and *animal welfare* while reducing the selection, emergence and spread of antimicrobial-resistant bacteria in *animals* to:

1. ensure the rational use ~~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 resistant micro-organisms and/or resistance determinants ~~(with their any resistance determinants)~~ within animal populations, their environment and from animals to humans;
- ~~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. contribute to maintaining the efficacy and usefulness of antimicrobial agents used in animal and 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 agents drugs, and the ability to transfer antimicrobial drug resistant micro-organisms to humans.~~

Article 6.9.3.

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* and all the other relevant stakeholders.

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 on the basis of the data submitted by the pharmaceutical industry and only if the criteria of safety, quality and efficacy are met. An evaluation 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 agents 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 target species, route of administration, dosage regimens ranges or and different durations of treatment that are proposed.

3. Market approval

Regulatory authorities should ensure attempt to expedite that the market approval process of a new VMPs containing antimicrobial agent(s) occurs without undue delay in order to address a specific need for the treatment of *animal* disease.

4. Registration procedures

The Competent Authority should establish and implement efficient statutory registration procedures that evaluate the quality, safety and efficacy of the VMPs containing antimicrobial agent(s). According to Article 3.1.2. of Chapter 3.1. of the Terrestrial Code, such Authority should be free from any commercial, financial, hierarchical, political or other pressures which might affect their judgement or decisions.

Member Countries are encouraged to apply the existing guidelines established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

Member 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 Member eCountries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of unlicensed and counterfeit ~~bulk active pharmaceutical ingredients and products~~ including bulk active ingredients.

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 spectrum ~~range~~ of activity of *antimicrobial agents* on both pathogens and non-pathogens (commensals);

- assess the capacity ~~ability~~ of the *antimicrobial agent* to select for resistance *in vitro* and *in vivo*, taking into consideration intrinsically resistant and pre-existing resistant strains;

- establish an appropriate dosage regimen (dose, dosing interval and duration of the treatment) and route of administration 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;
 - distribution concentration of the antimicrobial agents in the treated animal at the site of infection and concentration at the site of infection ~~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 in the target animal species 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 (VICH GL-9);
- 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 agents to select for resistance

Other studies may be requested in support of the assessment of the potential of antimicrobials agents to select for resistance (Guidelines providing information for developing such studies are available, e.g. VICH GL-27). 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) Pathway for the human exposure to antimicrobial resistant micro-organisms ~~the route and level of human exposure to food borne or other resistant organisms;~~
 - c) the degree of cross-resistance within and between ~~the class of antimicrobials classes and between classes of antimicrobials;~~
 - d) the intrinsic and 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 agents compounds in food producing animals
- a) When setting the acceptable daily intake (ADI) and MRL for an antimicrobial agents ~~substance~~, the safety evaluation should also include the potential biological effects on the intestinal flora of humans (Guidelines are available, e.g. VICH GL-33).
 - 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 ensure produce food in compliance with the MRLs, taking into account:
 - i) the MRLs established for the *antimicrobial agent* in the target animal and target tissues ~~under consideration~~;
 - ii) the composition of the product and the pharmaceutical form;
 - ~~iii) the target animal species;~~
 - ~~iiii) the dosage regimen and the duration of treatment;~~
 - iv) 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 (Guidelines are available, e.g. VICH GL-6 and GL-38). 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 medicinal products containing antimicrobial agent(s) product

The summary of product characteristics contains the information necessary for the appropriate use of VMPs containing veterinary antimicrobial agent(s) 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 as appropriate age or production category;
- e) therapeutic indications;
- f) target micro-organisms;
- g) dosage regimen and ~~administration~~ route of administration;
- 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 agent 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 if possible. This ~~Such a surveillance~~ will also contribute to general epidemiological surveillance of antimicrobial resistance.

12. Supply and administration of the veterinary medicinal products containing antimicrobial agent(s) 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 VAMPs containing antimicrobial agent(s).

13. Control of advertising

All advertising of antimicrobials agents should be compatible with the principles of responsible and prudent use and should be controlled by ~~a~~ codes of advertising standards, and the relevant authorities must ensure that the advertising of ~~antimicrobial~~ these 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 agents 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 preserving the effectiveness of antimicrobial agents and include:

- a) information on *disease* prevention, ~~and~~ management and mitigation strategies;
- b) the ability of antimicrobials agents to select for resistant micro-organisms and the relative importance of that resistance to public and animal health 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 with regards to veterinary medicinal products containing antimicrobial agent(s)

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 data.

2. Marketing and export of VAPs

For the marketing and export of VMPs containing antimicrobial agent(s) VAPs:

- a) only licensed and officially approved VMPs containing antimicrobial agent(s) 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 respect principles of responsible and prudent use and should comply with established codes of advertising standards, including to:

- a) distribute ~~disseminate~~ information in compliance with the provisions of the granted authorisation;
- b) discourage ~~ensure that~~ the advertising of VMPs containing antimicrobial agent(s) 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. Distributors of ~~Retailers distributing~~ VAMPs containing antimicrobial agent(s) 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 and prudent use of VMPs containing antimicrobials agent(s) 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) expiration date;
 - g) quantity supplied.
3. Distributors should also be involved in training programmes on the responsible and prudent use of VMPs containing antimicrobials agent(s) antimicrobials, as defined in point 14 of Article 6.9.3.

Article 6.9.6.

Responsibilities of veterinarians

The ~~concern of the veterinarian's responsibility~~ is to promote public health, ~~and~~ animal health and ~~welfare~~. ~~The veterinarian's responsibilities including~~ identification ~~preventing, prevention~~ identifying and treatment of 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 and taking into consideration the OIE list of antimicrobials of veterinary importance;
- b) make an appropriate choice of ~~the~~ antimicrobial agent based on treatment experience and diagnostic laboratory information (pathogen isolation, identification and antibiogram) where possible 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) known pharmacodynamics including the activity towards the pathogens involved;
 - iii) the appropriate dosage regimen and 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. In the absence of such results, an appropriate antimicrobial agent belonging to a different class should be used.

~~To minimise the likelihood of antimicrobial resistance developing in target or other organisms, it is recommended that antimicrobials agents 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 agents should be scientifically supported. Combinations of antimicrobials agents may be used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

3. Appropriate use of the VMPs containing antimicrobial agent(s) chosen

A prescription for VMPs containing antimicrobial agent(s) ~~antimicrobial agents~~ should indicate precisely the treatment dosage regimen, ~~the dose, the treatment intervals, the duration of the treatment,~~ the withdrawal period where applicable and the amount of VMPs drug to be provided delivered, depending on the dosage and the number of *animals* to be treated.

The off-label use of ~~a veterinary~~ VMPs containing antimicrobial agent(s) 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 dosage regimen and therapeutic regimen, the route of administration, ~~and the duration of the treatment.~~

4. Recording

Records on VMPs containing veterinary antimicrobial agent(s) drugs should be kept in conformity with the national legislation. Information records should include the following:

- a) quantities of VMPs medication used per animal species;
- b) a list of all VMPs medicines supplied to each food-producing animal holding;
- c) treatment schedules including animal identification and withdrawal period ~~a list of medicine withdrawal period~~;
- d) ~~a record of~~ antimicrobial susceptibility ies data;
- e) comments concerning the response of *animals* to treatment 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 VMAPs containing antimicrobial agent(s) to ensure compliance with their directions/prescriptions and use these records to evaluate the efficacy of treatments regimens.

5. Labelling

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

6. Training/continued professional development

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 and prudent use of VMAPs containing antimicrobial agent(s) (e.g. Guidelines for the judicious use of antimicrobials in various animal species developed by the American Veterinary Medical Associations).

Article 6.9.7.

Responsibilities of food-animal producers

1. Food-animal producers with the assistance and guidance of a *veterinarian* are responsible for implementing animal 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 (e.g. feedlot health plans, mastitis control plans, endo- and ectoparasite control and vaccination programmes, etc.);
 - b) use VMPs containing antimicrobial agent(s) ~~antimicrobial agents~~ only on veterinary prescription, and according to the provisions of the prescription;
 - c) use VMPs containing antimicrobial agent(s) ~~antimicrobial agents~~ in the species, for the uses and at the dosages on the approved/registered labels and in accordance with product label instructions, including maintenance of the storage conditions as appropriate, 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;~~
 - ef) address on-farm biosecurity measures ~~hygienic conditions~~ and take basic hygiene precautions as appropriate regarding contacts between people (~~veterinarians, breeders, owners, children~~) and the *animals* treated;
 - fg) comply with and record the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;
 - gh) dispose of un-used and expired surplus VMPs containing antimicrobial agent(s) ~~antimicrobials~~ under safe conditions for the environment; ~~medicines~~ they 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;~~
 - hi) maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the *veterinarian* responsible for treating the *animals*;
 - ij) keep adequate records of all VMPs containing antimicrobial agent(s) ~~medicines~~ used, including the following:
 - i) name of the product/active substance, ~~and~~ batch number and expiry date;
 - 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 (including date of the end of the withdrawal periods);
- viii) result of laboratory tests;
- ix) effectiveness of therapy;
- j~~k~~) inform the responsible *veterinarian* of recurrent *disease* problems.

3. Training

Food-animal producers should participate in the training programmes as defined in Point 14 of Article 6.9.3. It is recommended that food-animal producer organisations work in cooperation with the veterinary professional organisations to implement existing guidelines for the responsible and prudent use of VMPs containing antimicrobial agent(s).