# GOOD MANAGEMENT PRACTICE FOR BREEDING FARMS AND RATIONAL USE OF MEDICINAL PRODUCTS

## 1. A CHOICE INVOLVING ETHICS AND SOCIAL RESPONSIBILITY

In recent years, the massive use of antimicrobials in human and veterinary medicine has accelerated the emergence and spread of resistant microorganisms. The situation has worsened due to a lack of investment in the development of new effective antibiotics. The scale of the problem is shaped by the fact that more than 25,000 people in the European Union die each year from infections caused by antibiotic-resistant bacteria.

Antibiotic resistance is a natural biological phenomenon that occurs due to the emergence and propagation of bacterial antibiotic resistance factors and is triggered and amplified by the selective pressure exerted on microbial populations through the use of these drugs.

At national level, sectoral legislation has been already passed rendering punishable the improper use of veterinary medicinal products (the use of a veterinary medicinal product in a way that does not comply with the indications of the summary of product characteristics; the term also refers to serious abuse or incorrect use of a veterinary medicinal product) pursuant to art. 108, paragraph 9 of Legislative Decree 193/2006 (*Unless the fact constitutes a crime, anyone who does not comply with the requirements imposed by the authorisations issued pursuant to this decree shall be subject to the payment of an administrative fine ranging from €2,582.00 to €15,493.00*). Any drug for veterinary use must be used responsibly, based on the animal's examination by the veterinary surgeon who establishes the diagnosis and personally prescribes the type of medicinal product authorised for that animal species necessary to treat the ascertained pathology. Responsible use of the drug involves several entities: pharmaceutical companies, the manufacturer, the public veterinary service, the self-employed veterinary surgeon, and the breeder.

Responsible use therefore concerns all the subjects who intervene, in different ways, in the administration cycle.

- Veterinarians must choose the most appropriate medicinal products carefully and supervise their use.
- The breeder must promptly identify disease scenarios and ensure the correct use of prescribed medicinal products. The breeder must, in fact, regularly monitor the health and well-being of his/her animals, since any changes detected in the animals' health is essential for early diagnosis by the veterinary surgeon.

## 2. DEFINITION OF ANTIMICROBIAL

The term "antimicrobial" has been used in general and includes antibiotics and antibacterial agents, but excludes antivirals and pesticides. This definition is consistent with the wording adopted by the European Food Safety Authority, the European Centre for Disease Prevention and Control, the European Medicines Agency and the Scientific Committee on Emerging Health Risks; these definitions have been recently included in the joint scientific opinion on antimicrobial resistance focused on infections transmitted to humans from animals and food (zoonoses). See notes 1-2-3.

*(1) "Antimicrobial agents: any substance of natural, semi-synthetic or synthetic origin which, at in vivo concentrations, kills microorganisms or inhibits their growth by interacting with a specific target". Guidelines for the analysis of risks related to foodborne antimicrobial resistance (CAC/GL 77-2011).*

*(2) "An antimicrobial agent means a naturally occurring, semi-synthetic or synthetic substance which exhibits antimicrobial action at in vivo concentrations (kills microorganisms or inhibits their growth). Anthelmintics and substances classified as disinfectants or antiseptics are excluded from this definition." Health code for terrestrial animals.http://web.oie.int/eng/normes/mcode/en_glossaire.htm#terme_antibiotique*

*(3) An active substance of synthetic origin or of natural origin which destroys bacteria, inhibits their growth or their ability to reproduce in animals or humans, excluding antivirals and pesticides. http://www.efsa.europa.eu/it/efsajournal/pub/1372.htm*

## 3. PURPOSE

Given that antimicrobials are essential for the health care and health of animal and livestock populations, these guidelines aim at providing operational guidelines for the implementation of strategies to promote the cautious use of antimicrobials, in particular antibiotics, and to gradually reduce their use.

The ultimate goal is to reduce the need of antimicrobials for disease prevention. Animal diseases and infections must be primarily prevented by ensuring biosecurity, following good production and management practices, and implementing integrated disease control programs to minimize their onset and eradicate endemic diseases.

The aforementioned plan focuses on the following cornerstones:

- Staff training
- Breeding farm health management: prevention of viral and bacterial infections by drawing up a vaccination plan
- Adoption of good farming/biosecurity practices
- Respect for animal welfare
- Cautious use of antimicrobials
- Pharmacovigilance

## 4. STAFF TRAINING

The staff handling the animals must be sufficient and properly trained so that they can acquire professionally adequate skills, knowledge and competence.

We do not recommend entrusting occasional inexperienced workers with tasks entailing a responsibility in the management of animals; the person in charge of hiring the animal guardians must first make sure that the staff have received instructions and guidance on the main requirements related to the good farming practice, both in the legal and zootechnical fields.

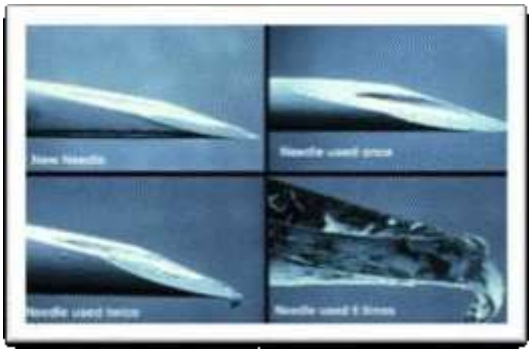
All staff must be supervised during the course of the training.

The correct practices are reminded through special forms to be completed by the farm's veterinary surgeon and posted near the medicine cabinet.

The workers must also be appropriately trained in the administration of medicinal products:

- *Correct storage of the medicinal product, preferring the use of disposable material or otherwise*:

- change the needle frequently in order to always use a very sharp needle for the treatments;



- rinse the syringe when the active ingredient is changed in order to avoid mixing;
- disassemble and wash the syringe daily with only hot water without using soap or other disinfectants that could interact with the active ingredients used;
- do not use the same syringe for vaccines and other types of veterinary drugs.

- *Adding medicinal products to milk in the case of a group treatment*:
  - Always dissolve the medicinal products first before adding them to the milk.
  - Do not mix more than one medicinal product in the mixer at a time.
  - Do not add medicinal products when the milk temperature exceeds 50 °C.
  - Mix for at least 1 minute after adding the medicinal products to the milk.
  - After treatment, properly wash the equipment in which the medicinal product was prepared before administering the untreated milk to another group of animals.

## 5. BREEDING FARM HEALTH MANAGEMENT: PREVENTION OF VIRAL AND BACTERIAL INFECTIONS BY DRAWING UP A VACCINATION PLAN

In order to control the spread of infectious diseases, each breeding farm should have a vaccination plan developed by the farm's veterinary surgeon, taking into account the viruses and bacteria identified in the farm.

*Vaccines have 2 main effects, both decisive, for the purpose of reducing the consumption of antimicrobials:*

- *they make animals less susceptible to contracting the infection and manifesting the disease, with a consequent improvement in productive and reproductive performance;*
- *they increase the immunity of the herd, with less circulation of infectious agents and a consequent improvement of the general health of the animals.*

In this case, at least the following aetiological agents must be taken into consideration, which may be the primary cause of disease or be the door opener for the irruption of secondary microorganisms:

- Parainfluenza 3
- Infectious bovine rhinotracheitis
- Viral diarrhoea
- Respiratory syncytial virus
- Histophilus somni
- Mannheimia haemolytica
- Pasteurella multocida
- Clostridium spp.

For administering the first vaccine, the vaccination plan should strongly recommend the use of live-attenuated vaccines, whenever possible, as these guarantee a greater and faster immune stimulation compared to their inactivated counterparts, with boosters after 3-4 weeks as provided by its MA.

The vaccines must be stored according to the temperatures indicated on the package leaflet and the cold chain must be preserved; for said purposes, the vaccines must be purchased from authorised suppliers and farm workers must be equipped with suitable isothermal containers to reduce thermal stress of the products during routine vaccination operations.

In order to guarantee the best conservation, vaccines should be purchased in the adequate quantity for the foreseen vaccination procedure to avoid storing high quantities for long periods.

## 6. ADOPTION OF GOOD FARMING/BIOSECURITY PRACTICES

Supplier farms are requested to adopt a Manual of good practices for the correct management of the breeding farm.

Particular attention must be paid to the hygiene of the facilities (including the animal housing boxes) and to the daily inspection of all the animals present.

In order to lower and restrict bacterial concentration, and to avoid the spread of infectious diseases, both the bedding and the manger should be kept clean, always making sure that the drinking troughs are thoroughly cleaned.

Before introducing new animals, it would be advisable, where possible, to carry out a sanitary vacuum along with an thorough disinfection of the box using suitable disinfectants (see Table 1.).

Table 1. Characteristics of disinfectants

| Active substance | Usage | Effectiveness | Disadvantages |
|---|---|---|---|
| Chlorhexidine | Equipment, premises, foot baths | Active on some species of bacteria and viruses | Reduced activity against some agents (some viruses, Pseudomonas) |
| Phenols | Equipment, premises, foot baths | Active on many species of bacteria | Limited effect on fungi, viruses, and bacterial spores. Possible environmental damage |
| Formaldehyde and other aldehydes | Equipment, premises, foot baths | Active on many species of bacteria, bacterial spores, fungi and viruses | Use as per indications due to high toxicity |
| Iodophors | Clean equipment | Active on bacteria and fungi | Inactivated by organic material.<br>Limited effect on bacterial spores and viruses |
| Inorganic compounds of hydrogen peroxide | Clean equipment and surfaces | Active on many species of bacteria, viruses, fungi and bacterial spores | Inactivated by organic material |
| Quaternary ammonium salts | Clean equipment | Active on many species of bacteria | Inactivated by organic material<br>Limited effect on bacterial spores, fungi and viruses |
| Chlorine, hypochlorite, chloramines | Clean equipment | Active on bacteria and fungi | Inactivated by organic material.<br>Irritating and corrosive.<br>Limited effect on bacterial spores and viruses |
| Calcium hydroxide | Rooms, bedding, floor cracks | Active on bacteria and viruses | Caustic for wet skin (especially nipple skin) |

In order to efficiently control the development of infectious/contagious diseases, an accurate inspection of all the animals in the farm at least twice a day is required in order to ensure an adequate therapy for all sick animals.

Biosecurity measures must be taken to protect the farm from biological agents which can be viral, bacterial, fungal or parasitic.

It is based on the implementation of written plans and good practice rules, both by farm operators as well as by visitors and all vehicles that enter the farm.
In fact, access to the farm centre is allowed only to authorised personnel; any guests must park their vehicles outside the entrance gate and be escorted inside while wearing disposable shoes and gowns before entering the sheds.

Lorries loading dead animals must wait outside the farm boundaries; if possible, the dead animal destined for destruction must be carried in closed containers to the outside of the farm.

The biosecurity measures must also include the pest control plan, with particular focus on rodents, flying insects and crawling insects.

7. RESPECT FOR ANIMAL WELFARE

The implementation of the legislation on animal welfare is the basis of the good management of the breeding farm. In addition to the regulatory points detailed in the EU regulations, animal welfare is promoted through the following premises:

- Form groups of animals that are as homogeneous as possible, based on sex, age, breed, origin, morphology, etc.
- Reduce animal density as much as possible: it should be born in mind that, as animals increase, there is a simultaneous increase in competitiveness; therefore, it is advisable to form small groups with no more than 20 animals.
- Avoid stressful events or practices while moving the animals.

In addition to these management points, there are other structural elements that should not be underestimated, such as:

- number of drinking troughs
- sufficient space in the manger to allow all animals to eat at the same time
- adequate ventilation
- adequate room temperature

8. CAUTIOUS USE OF ANTIMICROBIALS

The use of antimicrobials in animals must comply with the requirements of national and EU regulations.

In particular, the use of antimicrobials must comply with the information specifications of the authorised product [summary of product characteristics (SPC), package leaflet and labelling].

One of the fundamental aspects underlying the cautious and responsible use of antimicrobials is based on the targeted use, based on a clinical and possibly aetiological diagnosis, with the aim of:

- improve the efficacy of antimicrobial therapy;
- reduce the consumption of antimicrobials, avoiding their unjustified use;
- avoid unnecessary and unjustified expenses for the breeder;
- contribute to the containment of antimicrobial resistance.

For this purpose, the breeder and breeding staff must regularly supervise the animals so as to early detect signs of disease, injuries or abnormal behaviour.

In the event that an issue is detected, whether related to a single animal or to the breeding process, the farm's veterinary surgeon must be promptly involved in the necessary investigations, which include at least:

- clinical examination of the affected animals;
- specific diagnostic tests, aimed at identifying the cause (in the case of infectious diseases, the aetiological agent).

In cases where antimicrobials must be used to safeguard the health and welfare of the animals, the following principles must be respected:

- If it is necessary to prescribe an antimicrobial, the prescription should be based on a diagnosis made after a clinical examination of the animal by the prescribing veterinary surgeon.
- Rely on laboratory investigations as much as possible.
- Antimicrobial metaphylaxis (4) should only be prescribed when there is a real need for medical treatment. Antimicrobial metaphylaxis should never be used as a substitute for good management practices:

  *(4) The term 'metaphylaxis' refers to the simultaneous administration of the product to a group of clinically healthy (but presumably infected) animals in contact to prevent them from developing clinical symptoms and to prevent further spread of the disease. The presence of the disease in the group/herd must be ascertained before using the product. A metaphylaxis request should always be associated with a treatment request (EMA/CVMP/414812/2011-Rev.1).*

- Whenever possible, the administration of antibiotic medicinal products to an entire breeding farm or herd should be avoided. Sick animals must be isolated and treated individually (e.g. by administering injectable preparations).
- Opt for molecules with a more limited spectrum. (Broad-spectrum antimicrobials in fact lead to the development of resistance in non-target microorganisms more rapidly than antimicrobials with a more limited spectrum of activity. Only as a last resort, use the so-called "critically important antimicrobials" (CIAs) for human health (third and fourth generation cephalosporins, macrolides, fluoroquinolones and colistin).
- The medicinal product must be stored away from sources of heat, intense light and humidity, in a suitably clean place with restricted access.

The correct use of AM implies the compliance with:

- pharmacological criteria:
  - Pharmacokinetics (ability of the drug to penetrate in vivo into the infection site tissue)
  - pharmacodynamics (bacteriostatic/bactericidal)
  - combination of several active ingredients (See Table 2.)

Table 2. Combination of active ingredients

| COMBINATIONS | PREDOMINANT EFFECT |
|---|---|
| Beta-lactam antibiotic + Aminoglycosides | Synergism |
| Amoxicillin + Clavulanic Acid | Synergism |
| Sulphonamide + Diaminopyrimidine | Synergism |
| Beta-lactam antibiotic + Fluoroquinolones | Synergism/indifference |
| Beta-lactam antibiotic + Phenicol | Antagonism |
| Beta-lactam antibiotic + Tetracyclines | Antagonism |
| Fluroquinolones + Phenicol | Antagonism |
| Fluroquinolones + Tetracyclines | Antagonism |

*(Ref.: Antibiotic resistance: pharmacovigilance and the role of the veterinary surgeon. Turin, 8 October 2015. Prof. Giovanni Re. Modified)*

Combinations of AM guarantee a broader spectrum antibiotic coverage for the animal and reduce the toxicity of some active ingredients (e.g.: sulphonamides) and, more importantly, can limit the onset of AMR.

To this end, random AM combinations not based on compliance with the pharmacokinetic and pharmacodynamic criteria must be avoided by resorting to the relevant pharmacological guidelines or to preparations already available on the market.

According to the above, combining AM with the same pharmacodynamics (bacteriostatic with bacteriostatic and bactericidal with bactericide) is a good option since bacteriostatic agents antagonise the effect of bactericides, especially if the latter act on bacteria in the logarithmic phase of growth (e.g.: beta-lactam antibiotics).

Furthermore, the association of a time-dependent bactericide and a concentration-dependent one with a post-antibiotic effect (PAE) and with advantageous kinetics can develop a synergistic effect.

The association of AMs showing antagonism, in addition to favouring the onset of AMR and not being ethically correct, constitutes a useless use of the drug; therefore, it generates a both direct economic cost for the breeder linked to the use of a greater quantity of product, and an indirect cost, as the reduction in efficacy causes the onset of subclinical or chronic infections (greater losses in the barn).

- Compliance with the dosage and the provisions of the MA ("intra-label" use)

*Each antibiotic-based veterinary medicinal product should be used only according to the dosage and methods of administration indicated in the package leaflet and limited to the indicated microorganisms* (*Legislative Decree No. 193 of 6 April 2006*).

It is therefore requested to follow the treatment cycles provided for by the dosage of the medicinal product. The main good practices are:

- Discourage the use of the antibiotic in ways other than those indicated in the dosage ("extra-label" use).
- Avoid mixing products in the same syringe unless otherwise specified by the MA.
- Respect the correct time interval between administrations.
- Respect the duration of the treatment.
- Respect the quantity of active ingredient.
- Carefully estimate the animal's live weight.

Underdosage, i.e. reducing the effective dose, leads to a drop below the MIC90 (the lowest concentration of antibiotic capable of inhibiting the development of 90% of the bacterial strains tested), aggravating the AMR phenomenon. Nevertheless, it must be acknowledged that overdose can have even worse consequences by selecting resistant, often pathogenic, bacteria.

The use of electronic systems is recommended for the management of veterinary medicinal products logbooks on the breeding farm. These have the following advantages:

- Reduction of the margin of error in checking suspension times
- Alignment with the new electronic receipt rules being implemented
- Possibility of collecting and adding data for statistics and reduction objectives

- Antimicrobial sensitivity test

In order to define suitable therapeutic protocols, a constant collection of data relating to circulating microbial agents in the breeding farm must be carried out, evaluating the spectrum of sensitivity towards antimicrobials.
The evaluation of sensitivity to antimicrobials in vitro is based on both qualitative (diffusion in agar according to the Kirby-Bauer method) and quantitative methods, with evaluation of the minimum inhibitory concentration (MIC, agar diffusion test methods or microdilution in culture medium).
Regardless of the method used, the interpretation of the results of the sensitivity test requires the availability of breakpoints, provided by international organizations such as the Clinical Laboratory Standard Institute (CLSI).
The agar diffusion test method (Kirby-Bauer), currently the most used one in the diagnostic routine to obtain useful indications for the therapeutic choice, classifies the pathogen as sensitive (S), intermediate (I) or resistant (R) towards the antimicrobial molecules tested.
With quantitative tests, where the result is expressed as MIC, it is also possible to make a comparison between the different molecules to which the pathogen is sensitive (evaluation of the breakpoint/MIC ratio), preferring the one with the highest result.
One of the problems, both for the requesting veterinary surgeon and for the laboratory, given the large number of specialities registered as per animal species, production line and device, is to define which active ingredients to include in the antibiogram.

For a greater method standardization, it is advisable to test a limited number of antimicrobials and to avoid, when possible, testing molecules of the same antimicrobial class with similar behavior in vitro.
For this purpose, on the recommendation of the Centro di Referenza per l'Antimicrobicoresistenza (CRAB) [Reference Centre for Antimicrobial Resistance] - IZS Lazio Toscana, the so-called "prototype" molecules have been identified, which better predict efficacy in vivo through their use in vitro.
Here we report some examples of "antimicrobial panels" that can be used in cattle according to the different pathologies and related etiological agents (see Table 3). Together with the result of the antibiogram, the laboratory must provide a key reference that relates the prototype molecule to the related molecules represented (see Table 4).

Table 3. Panel of antimicrobials for sensitivity evaluation of bacterial strains isolated from bovines

| Gram + mastitis | Gram - mastitis | Gram + Other pathologies* | Gram - Other pathologies** | Gram - respiratory |
|---|---|---|---|---|
| Ampicillin | Ampicillin | Nalidixic Acid | Nalidixic Acid | Nalidixic Acid |
| Cephalothin | Cephalothin | Ampicillin | Ampicillin | Ampicillin |
| Ceftiofur | Cefazolin | Cephalothin | Cephalothin | Ceftiofur |
| Enrofloxacin | Ceftiofur | Ceftiofur | Cephalothin | Enrofloxacin |
| Erythromycin | Enrofloxacin | Clindamycin | Enrofloxacin | Florfenicol |
| Kanamycin | Kanamycin | Enrofloxacin | Florfenicol | Gentamicin |
| Oxacillin | SXT | Erythromycin | Gentamicin | Kanamycin |
| Penicillin | Sulfamethoxazole | Florfenicol | Kanamycin | Spectinomycin |
| Pirlimycin | Tetracycline | Kanamycin | SXT | SXT |
| Rifampicin | | Oxacillin | Tetracycline | Tetracycline |
| SXT | | Penicillin | Tilmicosin | Tilmicosin |
| Sulfamethoxazole | | SXT | | |
| Tetracycline | | Tetracycline | | |
| Tilmicosin | | Tilmicosin | | |

*** Including respiratory diseases**

**** Excluding respiratory diseases**

Table 4. Prototype molecules used in bovine pathology

| Prototype molecule | Molecules represented by the prototype |
|---|---|
| Nalidixic acid | Nalidixic acid, Flumequine |
| Ampicillin | Ampicillin, Amoxicillin |
| Cephalothin | Cefalotin, Cefalexin, Cefapirin, Cefazolin, Cefacetrile, Cefalonium |
| Cefazolin *(Enterobacteriaceae)* | Cefalotin, Cefalexin, Cefapirin, Cefazolin, Cefacetrile, Cefalonium |
| Ceftiofur | Ceftiofur, Cefoperazone, Cefquinome |
| Enrofloxacin | Enrofloxacin, Danofloxacin, Marbofloxacin |
| Erythromycin | Erythromycin, Spiramycin, Tylosin, Tilmicosin, Tulathromycin |
| Florfenicol | Florfenicol |
| Gentamicin | Gentamicin |
| Kanamycin | Kanamycin, Neomycin, Framycetin |
| Oxacillin *(Staphylococcus)* | Oxacillin, Cloxacillin, Dicloxacillin, Nafcillin |
| Penicillin | Penethamate |
| Pirlimycin | Pirlimycin, Clindamycin, Lincomycin |
| Rifampicin | Rifampicin, Rifaximin |
| Spectinomycin | Spectinomycin |
| Sulfamethoxazole | All sulphonamides |
| SXT | All sulphonamides boosted with Trimethoprim |
| Tetracycline | All tetracyclines (Chlortetracycline, Oxytetracycline) |
| Tilmicosin *(Pasteurella and Mannheimia)* | Tilmicosin, Spiramycin, Tylosin, Tildipirosin |

➢ Criteria for choosing the antimicrobial

**Based on the EMA (European Medicines Agency) classification and the products on the market registered for bovine species, indicationsfor use have been drawn up.**

**The new EMA categorisation takes into consideration all classes of antibiotics and also evaluates risks for human health and veterinary therapeutic needs.**

**EMA classified antibiotics considering two main aspects:**

- **The risk of developing antimicrobial resistance, with consequences on public health;**
- **The need to use these antimicrobials in veterinary medicine.**

**Furthermore, AMEG (Antimicrobial Advice Ad Hoc Expert Group), a group that includes experts of both human and veterinary medicine, who help to give indications regarding public health implications in the use of antimicrobials; also, they consider the public impact of routes of administrations in selecting antimicrobial resistances.**

**Antimicrobials have been categorized into 4 classes, from A to D: Avoid, Restrict, Caution, Prudence (see Table 5).**

***"Categorisation of antibiotics used in animals promotes responsible use to protect public and animal health"***

- **Category A ("Avoid") includes antibiotics that are currently not authorised in veterinary medicine in the European Union (EU). These medicines may not be used in food-producing animals and may be given to individual companion animals only under exceptional circumstances.**

- **Category B ("Restrict") refers to quinolones, 3rd- and 4th-generation cephalosporins and polymyxins. Antibiotics in this category are critically important in human medicine and their use in animals should be restricted to mitigate the risk to public health.**

- **Category C ("Caution") covers antibiotics for which alternatives in human medicine generally exist in the EU, but only few alternatives are available in certain veterinary indications. These antibiotics should only be used when there are no antimicrobial substances in Category D that would be clinically effective.**

- **Category D ("Prudence") includes antibiotics that should be used as first line treatments, whenever possible. These antibiotics can be used in animals in a prudent manner. This means that unnecessary use and long treatment periods should be avoided, and group treatment should be restricted to situations where individual treatment is not feasible.**

## Table 5. EMA Antimicrobials categorization.

**Categorisation of antibiotic classes for veterinary use**
(with examples of substances authorised for human or veterinary use in the EU)

**A — AVOID**

- **Amdinopenicillins**: mecillinam, pivmecillinam
- **Carbapenems**: meropenem, doripenem
- **Drugs used solely to treat tuberculosis or other mycobacterial diseases**: isoniazid, ethambutol, pyrazinamide, ethionamide
- **Glycopeptides**: vancomycin
- **Ketolides**: telithromycin
- **Lipopeptides**: daptomycin
- **Glycylcyclines**: tigecycline
- **Monobactams**: aztreonam
- **Oxazolidinones**: linezolid
- **Phosphonic acid derivates**: fosfomycin
- **Rifamycins (except rifaximin)**: rifampicin
- **Riminofenazines**: clofazimine
- **Other cephalosporins and penems (ATC code J01DI), including combinations of 3rd-generation cephalosporins with beta lactamase inhibitors**: ceftobiprole, ceftaroline, ceftolozane-tazobactam, faropenem
- **Pseudomonic acids**: mupirocin
- **Carboxypenicillin and ureidopenicillin, including combinations with beta lactamase inhibitors**: piperacillin-tazobactam
- **Sulfones**: dapsone
- **Streptogramins**: pristinamycin, virginiamycin
- **Substances newly authorised in human medicine following publication of the AMEG categorisation**: to be determined

**B — RESTRICT**

- **Cephalosporins, 3rd- and 4th-generation, with the exception of combinations with β-lactamase inhibitors**: cefoperazone, cefovecin, cefquinome, ceftiofur
- **Polymyxins**: colistin, polymyxin B
- **Quinolones: fluoroquinolones and other quinolones**: cinoxacin, danofloxacin, difloxacin, enrofloxacin, flumequine, ibafloxacin, marbofloxacin, norfloxacin, orbifloxacin, oxolinic acid, pradofloxacin

**C — CAUTION**

- **Aminoglycosides (except spectinomycin)**: amikacin, apramycin, dihydrostreptomycin, framycetin, gentamicin, kanamycin, neomycin, paromomycin, streptomycin, tobramycin
- **Aminopenicillins, in combination with beta lactamase inhibitors**: amoxicillin + clavulanic acid, ampicillin + sulbactam
- **Cephalosporins, 1st- and 2nd-generation, and cephamycins**: cefacetrile, cefadroxil, cefalexin, cefalonium, cefalotin, cefapirin, cefazolin
- **Amphenicols**: chloramphenicol, florfenicol, thiamphenicol
- **Lincosamides**: clindamycin, lincomycin, pirlimycin
- **Pleuromutilins**: tiamulin, valnemulin
- **Macrolides**: erythromycin, gamithromycin, oleandomycin, spiramycin, tildipirosin, tilmicosin, tulathromycin, tylosin, tylvalosin
- **Rifamycins: rifaximin only**: rifaximin

**D — PRUDENCE**

- **Aminopenicillins, without beta-lactamase inhibitors**: amoxicillin, ampicillin, metampicillin
- **Aminoglycosides: spectinomycin only**: spectinomycin
- **Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)**: cloxacillin, dicloxacillin, nafcillin, oxacillin
- **Sulfonamides, dihydrofolate reductase inhibitors and combinations**: formosulfathiazole, phthalylsulfathiazole, sulfacetamide, sulfachlorpyridazine, sulfaclozine, sulfadiazine, sulfadimethoxine, sulfadimidine, sulfadoxine, sulfafurazole, sulfaguanidine, sulfalene, sulfamerazine, sulfamethizole, sulfamethoxazole, sulfamethoxypyridazine, sulfamonomethoxine, sulfanilamide, sulfapyridine, sulfaquinoxaline, sulfathiazole, trimethoprim
- **Tetracyclines**: chlortetracycline, doxycycline, oxytetracycline, tetracycline
- **Natural, narrow-spectrum penicillins (beta lactamase-sensitive penicillins)**: benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, benzylpenicillin, penethamate hydriodide, pheneticillin, phenoxymethylpenicillin, procaine benzylpenicillin
- **Cyclic polypeptides**: bacitracin
- **Nitroimidazoles**: metronidazole
- **Steroid antibacterials**: fusidic acid
- **Nitrofuran derivatives**: furaltadone, furazolidone

9. VETERINARY PHARMACOVIGILANCE

Definition: *set of activities carried out to monitor, evaluate and improve the quality, safety, efficacy of the medicinal product after the marketing authorisation.*

Pharmacovigilance allows for monitoring the safety of veterinary medicinal products, including antibiotics, after their marketing authorisation.

The task of pharmacovigilance is to ensure:

- the safe use of veterinary medicines in animals;
- the safety of food of animal origin;
- the safety for humans who come into contact with veterinary medicines;
- the safety for the environment.

Pharmacovigilance requires that any suspected adverse reaction, including for example a decrease in efficacy or lack of appetite, be reported by veterinary surgeons and pharmacists to the Ministry of Health and the regional pharmacovigilance centres, using a special report form.

The reporting form (Annex II of Legislative Decree 193/2006) is the fundamental document for transmitting the information. The type of information subject to pharmacovigilance is described below:

*Negative side effect:* any unintended effect of a medicinal product that occurs at normal doses and that is related to the chemical-physical properties of the medicinal product.

*Unexpected negative side effect:* harmful and unexpected reaction that is not mentioned among the pharmaco-toxicological characteristics of the medicinal product (it is the most important reaction to report).

*Decrease in efficacy:* decrease in the clinical efficacy of the treatment with the veterinary medicinal product compared to that expected according to the indications for use reported by the MA.

Pharmacovigilance objectives: *the set of preventive control actions implemented in the context of the production, distribution, possession, supply and use of veterinary medicinal products)*, which include:

- the study of the side effects of veterinary medicinal products on animals;
- the study of negative side effects on humans who (accidentally) come into contact with them;
- the study of the low efficacy phenomena of medicinal products;
- verification of the validity of waiting times;
- the study of any problems relating to the environment (ecotoxicity);
- the collection of information on the methods of prescription and use of medicinal products (off-label);
- new therapeutic indications.

For an adequate evaluation of the adverse reaction, it is crucial that the report form be completed in its entirety as detailed as possible and that any available laboratory data, results of post-mortem examinations, photographs and other relevant information, are attached to the form. Reporting forms should normally be submitted within six working days in case of serious adverse reactions and within fifteen working days in all other cases. Furthermore, the Ministry of Health has set up a new specific email box to facilitate the transmission of the reporting forms for all adverse reactions on animals and humans. farmacovigilanzavet@sanita.it

The reporting forms must be sent to:

UFFICIO IV ex DGSA [OFFICE IV ex DGSA] - Medicinali veterinari e dispositivi medici ad uso veterinario [Veterinary medicines and medical devices for veterinary use]

DIREZIONE GENERALE DELLA SANITÁ ANIMALE E DEI FARMACI VETERINARI [DIRECTORATE-GENERAL FOR ANIMAL HEALTH AND VETERINARY MEDICINAL PRODUCTS]

DIPARTIMENTO DELLA SANITÁ PUBBLICA VETERINARIA, DELLA SICUREZZA ALIMENTARE E DEGLI ORGANI COLLEGIALI PER LA TUTELA DELLA SALUTE [DEPARTMENT OF VETERINARY PUBLIC HEALTH, FOOD SAFETY AND CORPORATE BODIES FOR THE PROTECTION OF HEALTH]

Ministero della Salute [Ministry of Health]
Via Giorgio Ribotta n.5,

00.144 ROMA

Tel.: +39 0659946255 - Tel.: +39 0659946932 - Fax: 0659946949

Email: farmacovigilanzavet@sanita.it

This document represents a guide for the practical implementation of the principles for the responsibleuse of antibiotics, identified by the Ministry of Health.

| **PRINCIPLES FOR A RESPONSIBLE USE OF ANTIBIOTICS IN LIVESTOCKANIMALS** |
|---|
| Correct diagnosis |
| Acknowledged pharmacokinetics |
| Acknowledged immunocompetence state |
| Choice of the appropriate antibiotic |
| Correct dosage |
| Verification of results |
| *Ministry of Health* |