EPRUMA

European Platform for the Responsible Use of Medicines in Animals

Best-practice framework for the use of antibiotics in food-producing animals in the EU

Table of contents

Background

The European Platform for the Responsible Use of Medicines in Animals (EPRUMA) was established in 2005 with the mission of promoting the responsible use of medicines (as defined in Directive 2001/82/EC as amended by Directive 2004/28/EC) in animals in the EU.

EPRUMA partners include:

- veterinarians;
- farmers and agri-cooperatives;
- manufacturers of animal medicines and diagnostics;
- feed manufacturers;
- professionals working in animal health and sanitary security;
- professionals working in sustainable agriculture;
- pharmacists.

The purpose of this document is to contribute to the continued effectiveness of antibiotics by providing a framework describing best practice. Whilst the core concepts in this framework should apply, the document can be adapted to the specific requirements of a Member State. This would lead to a co-ordinated and integrated approach across the EU but tailored to the specific requirements of any individual Member State.

The EPRUMA initiative is intended to complement Integrated Farming (IF)* in terms of the judicious use of inputs in agriculture, as described in the EISA European IF framework**.

* Integrated farming is a whole farm management system that covers and goes beyond good agricultural and environmental conditions/cross compliance and encompasses aspects of farming providing farmers and consumers with the reassurance of animal health and welfare; food quality, safety and traceability; and the protection of the environment.

** EISA has developed a European IF framework which provides a definition and characterisation of IF in the form of a guideline for the sustainable development of agriculture.

1 Introduction

Good health is essential for welfare and for optimal animal performance. Disease control is therefore an essential part of any successful management programme. In turn, safe food is produced by healthy animals. Disease control is part of high quality food production.

Antibiotic medicines are valuable tools and are essential for the continuing health and welfare of animals. In addition, they also make a significant contribution to productive and efficient livestock farming.

The animal health industry continues to offer the veterinary profession and the livestock industry a wide range of antibiotic products with which to treat infectious bacterial diseases, and which contribute to animal welfare by preventing or alleviating pain and discomfort.

The nature of antibiotic medicines is that antibiotic resistance may occur, and so reduce the efficacy of the product. This underlines the necessity to use antibiotic products with care.

The administration of antibiotic compounds should be complementary to good farm-management practice and IF as described in the EISA framework, and properly designed vaccination programmes. Many disease conditions can be avoided or minimised by using management practices that significantly reduce exposure to disease-causing bacteria, optimising the environment for the animal, including good hygiene, nutrition and vaccination programmes.

Regulations allowing an antibiotic to be on the market

The authorisation process is an exhaustive investigation involving all aspects of a new product. It is based on trial results and data submitted by the applicant company to the competent authority.

The objectives of the authorisation process are to ensure:

2 What is an antibiotic and how is it made available?

The term 'antibiotic' is in most cases synonymous with 'antibacterial", and describes a substance that kills or inhibits the growth of bacteria.

Most are naturally produced by bacteria and fungi, others are man-made but have the same effect. Even today, most of the substances used are from natural origin and are produced through fermentation processes.

Many organisations still use the word "antimicrobial" to describe antibiotics. EPRUMA has adopted a more modern definition of antibiotic and antimicrobial which is similar to the one adopted by the Heads of Medicine Agencies.

Antimicrobials: a general term for any compound with a direct action on micro-organisms used for treatment or prevention of infections. Antimicrobials are inclusive of anti-bacterials, anti-virals, anti-fungals and anti-protozoals.

Anti-bacterials: compound with a direct action on bacteria used for treatment or prevention of infections.

Antibiotics: synonymous with anti-bacterials.

The first antibacterials used were sulphonamides and penicillin discovered during the 1930s. By the late 1940s the pharmaceutical industry had started to discover and select numerous individual compounds which inhibited or killed bacteria, thus extending the range of antibiotic classes.

Although individual compounds within a class tend to have similar properties, they can differ in terms of:

- Spectrum - the species of bacteria that can be controlled by the antibiotic;
- Pharmacokinetics - the absorption, distribution and elimination of the antibiotic in the body of the animal treated;
- Toxicity - the potential harmful side-effects of a medicine.

Now numerous classes are available for use in animals by various routes of administration, such as bolus, drench, feed, injection, intramammary, pessary, topical and water. The different classes available include aminoglycosides, cephalosporins, (fluoro)quinolones, macrolides, penicillins, phenicols, pleuromutilins, polypeptides,ionophores, sulphonamides, tetracyclines, to name just a few. Some of these families have been developed exclusively for animal health.

Before an animal medicine, including antibiotics, can be placed on the market a manufacturer must prove to the regulatory authority the quality, safety and efficacy of the product when used as recommended. These procedures are rigorous and allow the user and consumer to have confidence in licensed medicines. As with human medicines, the safety, quality and effectiveness of any medicine must be proven to the satisfaction of independent regulatory authorities.

- **Safety:** the product is safe for the animal itself, the consumer of food derived from treated animals, those handling the product and the environment,
- **Quality:** the product is of consistent high quality, does not deteriorate and has the stability to last at least until the expiry date, and,
- **Efficacy:** the product's efficacy conforms with the claims made on its information leaflet and label.

The authorisation process does not stop at this point. In addition, users are required to engage in:

- **Pharmacovigilance:** the systematic collection of information on any adverse effect that may be observed in the daily use of the product.

In order to continuously ensure the safety of animals, consumers, users and the environment, national authorities monitor for the presence of undesirable residues. In addition, many authorities monitor the quantities used and carry out surveillance of antibiotic resistance among relevant bacteria.

3 Ensuring animal health

Animal health starts with good husbandry practices.

Farmers should regularly monitor the health and welfare of their animals. Appropriate professional veterinary advice should be sought where necessary on the effective prevention, diagnosis and treatment of disease.

These key elements of animal health are in conformity with EISA's IF framework particularly chapter IX.

Management

Animal health is a precondition for animal welfare. A good welfare status will help the animal to maintain its natural resistance against diseases and good health is a precondition for the well being of an animal. Both health and welfare are much influenced by the way animals are kept and must be in compliance with existing EU legislation.

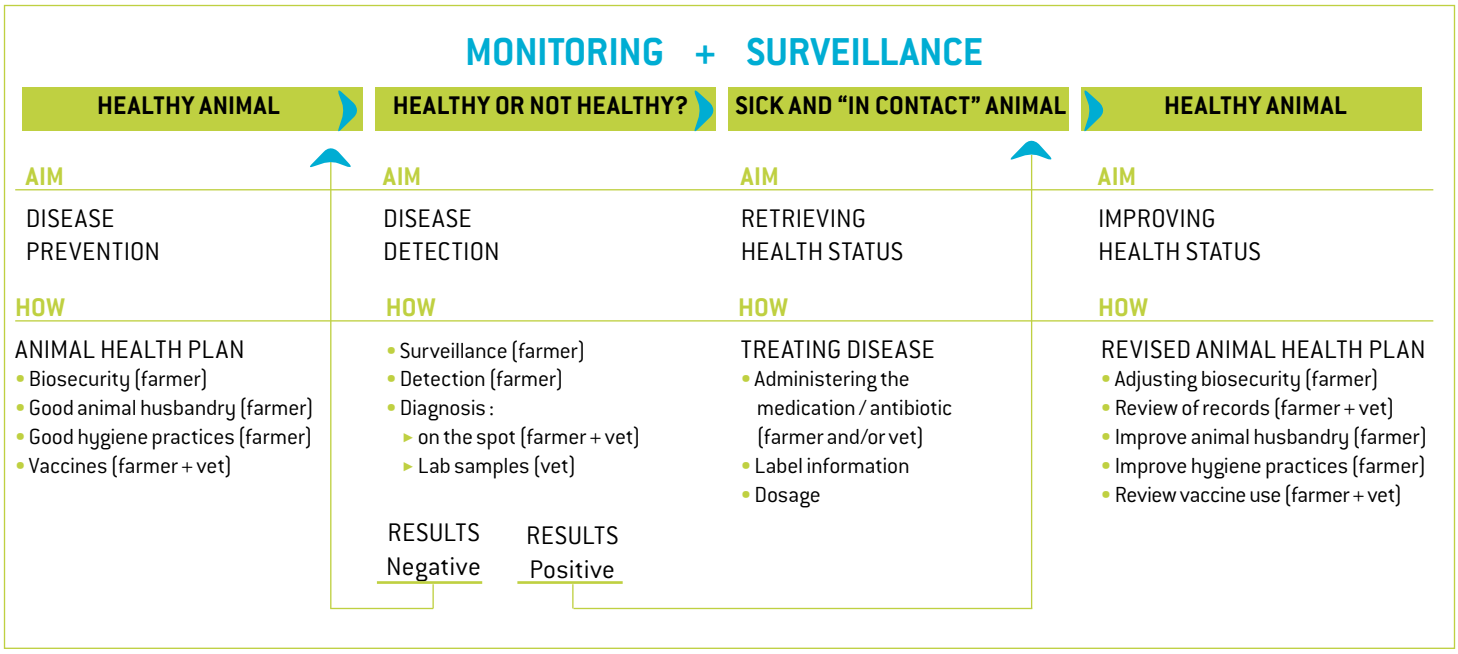
Environmental conditions including temperature, humidity, clean air and bedding, amount of light, etc. should be adapted to the animal's needs. Equally important are the availability of clean water, an adequate diet, and enough space to walk and rest. Stress should be avoided as it will have a negative effect on the animal's resistance against infections.

Furthermore, proper monitoring of the animals and keeping records of the observations made is essential for an early diagnosis of conditions affecting the animal's health or welfare. A well-designed animal health plan is a key element for every farm.

Biosecurity

A special point of attention in keeping animals free of infectious diseases is biosecurity.

The purpose of biosecurity is to minimise the potential for introducing disease-causing organisms onto the holding by e.g. newly purchased animals, people, vehicles and pets, to mention but a few. Relatively simple measures can be taken without excessive financial investments and these can be very effective and helpful in ensuring the health of animals. Even where a measure doesn't seem to be completely effective, it does not mean that it is worthless. A limited reduction of the risk of introduction of germs is still much better than no reduction at all.



Vaccines

Vaccines are very valuable tools in the prevention and control of many infectious diseases. They are safe and effective in enhancing animals' resistance against infections.

However, **there are several diseases for which no vaccines are (yet) available. In these cases other means of prevention and control, including the use of veterinary medicines, e.g. antibiotics, may be required.**

This applies for situations like:

- acute infections, which require immediate treatment;
- emerging diseases.

Acting through the natural immune system, their use should always be considered in the context of a broader strategy. Other measures, such as good hygiene, good animal husbandry and disease monitoring are equally important parts of disease-prevention programmes. The optimal strategy depends on the local situation on the farm, and also on factors such as area animal density, presence of pathogens in wildlife, availability of reliable tests, etc. Adequate monitoring of vaccinated animals is an essential part of a vaccination programme.

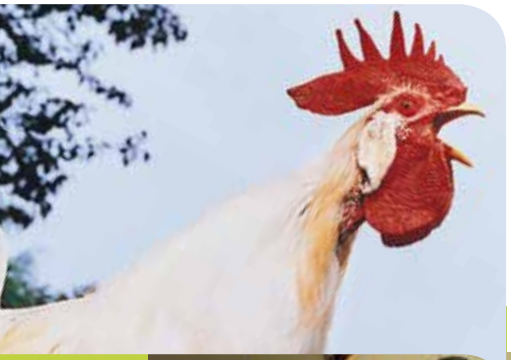
Veterinarian/farmer interaction (animal health plan)

An open communication between the farmer and the veterinarian is essential in order to achieve optimal animal health. Preferably, it should take place at regular intervals and not only when a problem occurs. When appropriate, other experts, such as those on housing, feed, nutrition, hygiene, etc., should be consulted.

The information obtained from the farmer together with the details obtained by the examination of the animals and local circumstances will allow the veterinarian to propose an optimal solution for a sustainable improvement of the animals' health and welfare. The records also assist the farmer in demonstrating compliance with good farming practice.

4 Diagnosing and treating disease

When a disease occurs, the veterinarian examines the animal(s) and the circumstances in which they are kept.



Disease diagnosis and treatment are closely linked.

When a disease occurs, the veterinarian examines the animal(s) and the circumstances in which they are kept. On the basis of this information s/he will diagnose the disease and decide on an intervention. This could be management advice on the way that the animals are kept (feeding/housing) or the prescription of a suitable (antibiotic) therapy. If necessary, whenever possible, a sample may be sent to a laboratory for analysis to establish the exact bacterium causing the disease and its sensitivity and so choose the most appropriate treatment. However, if laboratory confirmation is not possible, the choice of antibiotics is then a matter of experience and of clinical judgement based on the previous bacterial sensitivity on the farm in question. The veterinarian will evaluate the result of his/her treatment of choice and, if necessary, adjust this.

Frequently, animals are kept in groups and whilst this is beneficial from practical husbandry and animal welfare aspects, it means that the group may be at risk when a disease strikes. As a result, it is sometimes necessary to treat the group. This would be the case where it is known that an infectious disease is present and where experience shows that the disease will infect most, or even all of the animals in the group once one animal shows symptoms of infection. Such use is sometimes termed 'metaphylaxis'.

Bacterial infections in large flocks or herds often appear at identifiable and predictable stages during the life time of the animal, e.g. respiratory problems after regrouping, colibacillosis during the post-weaning period, shipping fever following transport, etc. Treating in situations like this is referred to as prophylactic treatment. **The farmer and the veterinarian are familiar with imminent disease hazards on their farms, and early action, carefully and selectively carried out, is a necessary part of disease management.**

As may be appreciated, preventative action is similar to that practiced in human medicine in cases such as bacterial meningitis outbreaks in schools or colleges where the group of students potentially exposed will be treated in a preventative manner.

Having taken a decision to treat with an antibiotic, the first consideration for a veterinarian is to select the most appropriate one. The next step is to use a specific authorised medicinal product based on the diagnosis made for the disease condition involved and

on the expertise of the veterinarian. A range of antibiotics are available and the veterinarian should use his/her professional knowledge in the context of a specific disease situation to choose the product with the most appropriate spectrum. (A range of products should be used over time to guard against the possible emergence of resistance.)

The continuous use of the same product for the same type of indication (e.g. respiratory, intestinal, systemic, etc.) over a long period of time should be viewed with caution, unless preliminary testing in the laboratory has shown satisfactory susceptibility of the bacteria involved. The veterinarian may use a range of products over time to guard against the possible emergence of resistance, sometimes known as a 'rotation programme' in order to safeguard long-term effectiveness and to minimise resistance selection pressure.

Several new products have been introduced over the years, and these have strengthened the therapeutic armoury of the veterinarian.

Antibiotics are critical when treating, preventing and controlling animal diseases. In managing animal diseases, veterinarians often focus on controlling the disease on a herd or flock basis. In human medicine, treatment with antibiotics is almost always directed at the individual. Like in the human sector, prophylactic or metaphylactic administration of antibiotics is a practice that has shown to be beneficial to maintaining herd or flock health, like in mastitis disease management. Availability of a variety of antibiotics is a critical concern to food-animal veterinarians.

It is necessary to have a wide range of safe and effective products from all antibiotic classes available to the veterinarian in treating animal diseases in order to discourage the potential selection of resistance by the overuse of a restricted number of products.

The farmer, the veterinarian and other experts must work together to ensure that the outcome of treatment is effective. The farmer may be required to administer subsequent treatments. Where this is the case, it is essential that all instructions are followed. The farmer should report any unexpected delay in recovery to the veterinarian. If necessary, an alternative form of treatment may be commenced if the animal is not responding as expected.

Veterinary surgeon to make final choice

Today, a broad range of antibiotics is available in the market. They vary in many different ways such as route for administration, speed and extent at which they are taken up by the animal, modes of action, speed and extent of penetration into the tissues, etc.

At the same time, micro-organisms vary in the way they are affected by the different antibiotics. For this reason, the selection of an antibiotic must always be based on several criteria, such as the micro-organism affecting the animal(s), the occurrence of resistance against antibiotics, the animal species, the way the antibiotic has to be administered, etc. The selection of the proper treatment must always be made by the veterinarian after examining the animals, the local situation and making a diagnosis.

Cascade

In exceptional cases, where no medicine is authorised, there is a possibility for the veterinarian to use, for example, products that are authorised in other EU countries or for other animal species. This exception exists to avoid unacceptable suffering of animals. In these cases the veterinarian has to follow specific steps, the so-called cascade, and s/he has to make sure that there is no risk for the animal(s) concerned and for consumers of food products of animal origin.

5 Effective administration of a medicine

Successful treatment is determined by proper administration of the antibiotic coupled with the correct quantity used for the necessary time period.

The dosage recommendation of an antibiotic medicine has been tested extensively by the company applying for an authorisation. The purpose is to ensure that the dose given is sufficient to ensure that the appropriate quantity of the antibiotic reaches the site of infection for a sufficient amount of time to ensure that the animal recovers from the disease.

Repeated administration may be necessary in order to reach clinical success. In the human medicine context, this is achieved by, for example, taking a tablet three times a day over seven days. For animals, the same principle applies.

As with human medicines, the label contains the necessary information for appropriate and safe use and storage.

Maximum residue limit

For food-producing animals, studies are required to see how quickly residues of the medicine are eliminated from the animal. **Maximum residue limits (MRLs) are established to set a maximum level of the antibiotic that may remain in the animal without posing a risk to consumers of produce taken from it.**

Withdrawal periods (the time between administration of the medicine and slaughter or the taking of food produce, e.g. milk or eggs) are then set to ensure that any remaining residues are below the MRL. Huge safety margins are built into the system to ensure that consumers are protected.

6 Record keeping

In relation to record keeping, in all EU Member States it is mandatory to maintain records for at least five years - irrespective of whether or not the animal is still on the farm - of all medicines used in food-producing animals, including antibiotic treatments.

In addition, it is recommended that the veterinarian, in co-operation with the farmer, keeps track of all the information related to infectious diseases on the farm. Historical information, including laboratory sensitivity data, is very valuable in planning future treatments.

For safe transport, storage and disposal of medicines, legislative requirements should be followed in all cases.

Records indicate the ongoing use of antibiotics on a farm. Trends should be observed and changes in use examined. Overall management conditions should be kept under constant review.

7 Protecting future effectiveness

Pharmacovigilance is the process whereby concerns in relation to safety or effectiveness of medicines are reported to the national authorities. Where a concern arises, the farmer should consult the veterinarian and a report of the incident should be submitted to the authorities if the veterinarian suspects that a safety or efficacy problem has arisen.

This system is very beneficial in allowing the ongoing monitoring of products in use under actual field conditions.

Monitoring sensitivity by the animal health industry

Resistance is a phenomenon in which certain bacteria stop responding to treatment by a specific antibiotic. Therefore, it is of great importance to monitor the sensitivity of bacteria to antibiotics on an ongoing basis. The monitoring of sensitivity is a complex operation which includes collection of representative samples and consistent evaluation of results.

The animal health industry is engaged in this type of activity, sometimes concurrently with the regulatory authorities or government agencies. The communication of information on levels of resistance will allow veterinarians to make informed decisions on which antibiotics they should use for the best chance of success. Moreover, monitoring antibiotic resistance in animal production is also relevant to public health.

The development of resistance

Antibiotics have activity against particular bacterial species or groups of species. Clinical trials will prove the effectiveness of a particular product against a particular bacterium. At the outset, very effective results should be achieved. However, any particular population of bacteria may be made up of different individuals with slightly different genetic properties. A few bacteria, making up a tiny fraction of the overall population, may have the natural ability to survive treatment with the antibiotic. The result may be that the resistant bacteria survive and become an increasingly dominant part of the population over time and in response to selective pressure imposed by the use of the antibiotic.

As time progresses, treatment may become less effective eventually leading to the situation where the product no longer effectively controls the disease. At this point, we have clinical resistance. As may be appreciated, this is usually a gradual process with samples showing increasing levels of resistance over time, although in some cases antibiotics may remain efficacious over many decades.

As an alternative, bacteria may mutate or acquire genetic material from other bacteria and develop the ability to survive treatment. In this case, the switch from susceptibility to resistance may be relatively rapid if the resistant bacteria multiply and spread rapidly. Most resistance emerges through this latter process.

Having developed resistance to one type of antibiotic, the bacteria may be resistant to related antibiotics in the same class of antibiotics. In some cases, bacteria may develop resistance to a number of separate classes and so become multiple resistant.

Conclusion

Antibiotics have a key role to play in protecting animal health and welfare. Protecting animals against disease contributes to the production of high quality food from healthy animals whilst minimising the impact on the environment.

A comprehensive regulatory process applies before these medicines may be placed on the market. Veterinary surgeons have the necessary detailed education to select the most appropriate medicine and to ensure safe use. The farmer has a key role to play in preventing disease and in ensuring that antibiotics are used correctly.

Antibiotics have revolutionised veterinary practice since their introduction more than 60 years ago. Many of these early medicines are still successfully used today although loss of efficacy through resistance development is an ever-present risk.

It is essential that all parties work together to ensure safe use and to minimise the development of resistance. A guiding principle with respect to antibiotics should be “As little as possible, as much as necessary” since we owe it to both present and future generations to use these agents with care and discrimination. In this way, those to come will benefit, as we have, from these valuable medicines.

EPRUMA partners

COPA/COGECA
European Farmers and Agri-Cooperatives

EGGVP
European Group for Generic Veterinary Products

EISA
European Initiative for Sustainable Development in Agriculture

EMVD
European Manufacturers of Veterinary Diagnostics

FECAVA
Federation of European Companion Animal Veterinary Associations

FEFAC
European Feed Manufacturers Federation

FESASS
European Federation for Animal Health and Sanitary Security

FVE
Federation of Veterinarians of Europe

IFAH-Europe
International Federation for Animal Health-Europe

PGEU
Pharmaceutical Group of the European Union

Associate partners

AMCRA

Centre for Expertise on Antibiotic Consumption and Resistance in Animals (Belgium)

RUMA

Responsible Use of Medicines in Agriculture Alliance (United Kingdom)

SDa

The Netherlands Veterinary Medicines Authority

VETRESPONSABLE

Platform for the Responsible Use of Medicines in Animals (Spain)

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