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ASEAN GUIDELINES FOR THE PRUDENT USE OF ANTIMICROBIALS IN LIVESTOCK

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OF
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INTRODUCTION

The Antimicrobial drugs are essential tools for the management of infectious diseases in animals and humans. In animal husbandry, antimicrobials are widely for animal therapy, disease prevention (prophylaxis), as growth promotants (to increase feed conversion, growth rate or yield) and for protozoal disease control (substances with antibiotic activity fed to livestock to control protozoal diseases such as coccidiosis).

However, the widespread and inappropriate use of antimicrobials in livestock is a contributing factor to the emergence and spread of antimicrobial resistance (AMR) in livestock. AMR threatens the livelihoods of farmers should diseases of livestock become untreatable due to resistance against therapeutic agents. Using antibiotics in animals may potentially cause resistance in foodborne pathogens such as *Salmonella* and *Campylobacter*, that could result in foodborne illnesses in humans that are more difficult to treat. It also poses a risk to public health through potential transfer of resistance genes to human pathogens, through contact with animals or through the food chain. Antimicrobial resistance therefore presents a threat to public health, animal health and economies.

The ASEAN Sectoral Working Group for Livestock (ASWGL) has identified antimicrobial resistance in livestock as a priority area for action. On 6 October 2016, in recognition of the need for a concerted regional effort to combat AMR in the agriculture sector, the ASEAN Ministers for Agriculture and Forestry at the 38th AMAF meeting agreed on cooperation to combat AMR¹, including the promotion of the prudent use of antimicrobials in livestock.

The prudent use of antimicrobials recognises the importance of antimicrobials in animal health, while ensuring sustainability by maximising their therapeutic effect and minimising the development of AMR through more rational and targeted use. Taking into consideration the occurrence of cross- and co-resistance, which mean that any exposure to antimicrobials increases the occurrence of AMR, the outcome of prudent use should be an overall reduction in the use of antimicrobials, and to prevent the overuse and misuse of antimicrobials, in particular, the classes of antimicrobials that are critically important to human health.

¹AMAF 38th, Joint Press Statement Para 7. “*Antimicrobial Resistance in Agriculture*: Recognising the expansive and adverse impact of Antimicrobial Resistance (AMR) in agriculture on public and animal health, livelihoods, food security and safety, we agreed to strengthen regional cooperation in AMR mitigation through: (i) Raising awareness and advocacy on AMR issues and promote the prudent use of antimicrobials; (ii) Enhancing capacities on surveillance, diagnosis and research on AMR and antimicrobial usage (AMU); (iii) Promote good animal husbandry practices and the development of viable alternatives; and (iv) Enhancing collaboration with relevant sectors and stakeholders including development partners and donor agencies.”

Prudent use extends beyond the administration of antimicrobials to animals. It includes implementing practical measures involving all stakeholders to improve animal health and welfare, ensuring the quality and effectiveness of antimicrobials when used, and reducing the need for antimicrobials through improving husbandry and biosecurity.

These guidelines form part of ASWGL's overall strategy on AMR, as set out in the ASWGL Specific Plan of Action for 2016-2020 and the ANFPVP Plan of Action 2016-2020, in accordance with cooperatives agreed at 38th AMAF.

SCOPE & PURPOSE

These guidelines on the prudent use of antimicrobials in livestock relate to how prudent usage can contribute to containing the development of AMR with the aim of protecting both animal and human health as well as the environment.

Part A describes some basic principles of prudent use, while Part B sets out more specific guidelines on antimicrobial use in livestock and the responsibilities of various stakeholders.

These guidelines should be used in conjunction with existing guidance documents provided by national authorities and other international standards and guidelines such as those developed by the OIE, WHO and the Codex Alimentarius Commission. These are referred to in the relevant sections of this document.

These guidelines are intended for consideration by ASEAN Member States for developing national strategies to combat AMR through the promotion of the prudent use of antimicrobials in their livestock sectors. National guidelines are likely to be more detailed and adapted to current regulatory systems, local circumstances, animal health status, disease control programmes and farming or veterinary systems and practices and available resources. National objectives may also be determined by the extent of the AMR problem in the country and assessment of the risk to public health. These guidelines are based on existing international guidelines, best practices and the current understanding of AMR, and should also be updated as new knowledge becomes available.

PART A: PRUDENT USE PRINCIPLES

Some Basic Principles

Antimicrobials are essential for the treatment of infectious diseases in livestock. However, any use of antimicrobials can lead to the development of AMR. The risk increases if such antimicrobials are used inappropriately, such as in an untargeted manner, at sub-therapeutic doses, repeatedly, or for inappropriate periods of time. Prudent use of antimicrobials refers to the usage of antimicrobials which maximises therapeutic effect and minimises the development of antimicrobial resistance. Prudent use of antimicrobials also takes into account measures to ensure the quality of antimicrobials used, their implementation when antimicrobial agents are administered to animals, and forms part of good veterinary and good agricultural practice. It also requires the cooperation and involvement of all stakeholders for successful implementation.

Prudent use measures are generally based on the following basic principles:

Principle 1: *The use of antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health and welfare.*

Principle 2: *The use of antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight and consultation.*

Principle 3: *Only antimicrobial agents meeting the criteria of safety, quality and efficacy should be used in food-producing animals, and used according to the approved and intended uses.*

Principle 4: *Use “as little as possible, as much as necessary”*

Principle 5: *Activities associated with the responsible and prudent use of antimicrobials involve all relevant stakeholders.*

Principle 6: *Prudent and responsible use of antimicrobials is part of good veterinary and good animal husbandry practice and takes into consideration disease prevention practices such as the use of vaccination and improvements in husbandry conditions.*

Principle 7: *Surveillance, monitoring and the collection of reliable data provide evidence to guide policies and inform on effectiveness of measures associated with prudent use of antimicrobials in livestock*

These are further discussed below.

Principle 1: The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health and welfare.

Antimicrobials are necessary to the health and welfare of animals. However, many antimicrobials used in animals are also used in humans. Some of these are critical for preventing or treating life-threatening infections in humans². The OIE list of antimicrobial agents of veterinary importance³ includes some considered to be critically important both for human and animal health (shared class antimicrobials), such as fluoroquinolones and the 3rd and 4th generation of cephalosporins.

This principle is that, medically important antimicrobials should be reserved for targeted treatment of disease to ensure the health and welfare of the animal, based on clinical diagnosis by a veterinary professional and, whenever possible, on the results of microbiological susceptibility tests, and using an antimicrobial agent of as narrow-spectrum as possible. In particular, the use of critically important antimicrobials in livestock increases the risk of resistance to antimicrobials essential for human health, and should be carefully considered before use. These should be used only when no other alternatives are available for assuring animal health and welfare.

It should be noted that the non-therapeutic use of antimicrobials, such as for growth promotion, in the absence of a risk analysis, is generally not considered responsible use of antimicrobials in food-producing animals. OIE⁴ recommends that such risk analysis should be based on scientific evidence; and focus on the potential to impact resistance to antimicrobials used in human medicine. Moreover, the development of roadmaps to phase out use of medically important antimicrobials as growth promotants, either through voluntary practice or legislation, will contribute towards the goal of ensuring the availability of effective medicines for treating diseases.

Part B Section I provides guidelines on the use and administration of antimicrobials in livestock, including special considerations for the use of critically important antimicrobials and for administration by feed and water.

Principle 2: *The use of antimicrobials in food-producing animals should be limited to those uses that include veterinary oversight and consultation.*

Many feed-use antimicrobial drugs are currently used in food-producing animals for treatment, control, prevention of disease and production purposes. Veterinary oversight, including prescription and consultation, is an important mechanism for helping to assure appropriate use of antimicrobials. Veterinarians (or other suitably trained person authorised to prescribe antimicrobials in accordance with national legislation) play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease. Responsible antimicrobial usage critically depends on the veterinary professional making a correct diagnosis such that appropriate treatment can be administered. The involvement of a veterinarian is key in the decision-making process regarding antimicrobial drug use. ASEAN GAHP guidelines for poultry⁵ specify that (i) the use of medicines must be under the supervision of veterinarian or competent authority, and (ii) the use of antibiotics or medicated feeds for disease control must be in accordance with the instructions of a veterinarian following country regulations. Part B Section II further describes the responsibilities of veterinarians (or authorised person) in prescribing antimicrobials. It is recognised that the nature and extent of veterinary involvement can vary due to numerous factors such as geographic location, resources and animal production settings. The development of appropriate national strategies and roadmaps to phase-in or strengthen veterinary oversight on the use of antimicrobials in livestock, especially medically important antimicrobial drugs, will be an important step towards prudent use of antimicrobials in livestock.

Principle 3: *Only antimicrobials meeting the criteria of safety, quality and efficacy are used in food-producing animals, and used according to the approved and intended uses.*

The use of safe, quality and effective veterinary medicinal products (VMP) ensures that the intended treatment is effective in controlling disease, while minimising adverse effects in the animal, to the consumer or the environment.

This may be achieved through establishing effective regulatory and control systems for antimicrobials used in agriculture to ensure that:

- antimicrobials available for animals are safe, effective, and of consistent and high quality;
- minimise the presence and use of fake, illegal or adulterated products that may be ineffective;
- accurate information is accessible by prescribers and users;
- access to these vital medicines is subject to effective, veterinary-guided oversight;

- veterinary medical products are stored and transported in a manner that maintains the effectiveness of the drug, such as ensuring cold chain where necessary;
- veterinary medical products are disposed appropriately to prevent contamination of the environment.

Safety ensures that antimicrobials authorised are safe for the user, the consumer and the environment. Safety assessments include: (i) assessing the toxicology of the product - understanding whether, and how the chemicals in the medicine could cause adverse reactions in the target species or in people, taking into account the way these chemicals cause changes to the normal biological functions of the body; (ii) setting a withdrawal period, if the antibiotic is to be used in a food-producing animal - this is the minimum length of time after treatment that must pass before an animal may go for slaughter or have its products, such as milk or eggs, considered to be safe for consumers².

Quality ensures that antimicrobials are manufactured to the high standard required. This will include ensuring that the applicant has demonstrated that: (i) the antibiotic is manufactured appropriately; (ii) the manufacturing process delivers a reproducible product; (iii) the medicine will perform as it should up to its expiry date².

Effectiveness ensures that antimicrobials will work against the microorganism causing illness in all of the animals the medicine is authorised to treat. This will include ensuring that the applicant has demonstrated: (i) that antibiotic resistance has been taken into account; (ii) that a correct dosage regimen has been set - how much, how often and for how long; (iii) that responsible use of antibiotics warning is on the product literature and data sheet (Summary of Product Characteristics)².

In general, an effective regulatory and control system to ensure safety, quality and effectiveness includes mechanisms for:

- registration and market authorisation of all antimicrobial products used for food animals and in agriculture;
- ensuring that all antimicrobial products used for food animals and in agriculture are of adequate quality and are manufactured according to good manufacturing practices;
- licensing of manufacturers, distributors, and personnel selling or prescribing any antimicrobial products used for food animals or in agriculture;
- combating the use of illegal, poor quality and prohibited drugs.

The OIE Terrestrial Code⁶ and Codex Alimentarius⁷ provide guidance on the registration and quality assurance of VMPs. Evaluation for purpose of registration may include an assessment of quality control, therapeutic efficacy and potential to select for resistance, establishment of acceptable daily intake (ADI), maximum residue limit (MRL) and withdrawal periods in food-

producing animals, list of product characteristics and post-marketing antimicrobial surveillance, among other aspects, as determined by national registration requirements. Countries lacking the resources to implement an efficient registration procedure for VMP containing antimicrobial agents, and which are importing them, could undertake the following alternative measures^{6,7}:

- a. evaluate the efficacy of administrative controls on the import of VMP;
- b. evaluate the validity of registration procedures of the exporting and manufacturing country as appropriate;
- c. co-operate with relevant authorities to check the quality of imported VMP as well as the validity of the recommended conditions of use.

Principle 4: Use “as little as possible, as much as necessary”

Antibiotics are essential to protect the health and welfare of animals, and should be used when needed. The overriding principle of antimicrobial prescribing is to “use as little as possible but as much as necessary” to address an infection.

Antimicrobials, when used responsibly: when they are needed, in the amount needed and under the supervision of a veterinarian, helps ensure greater animal health and welfare, and provide a safe and secure food supply. In this sense, it is crucial that antimicrobials are prescribed and administered at the correct dosage and following an accurate examination and clinical diagnosis, supported by sensitivity testing wherever possible. This can be summarised as the 5 R’s: Right drug, Right time, Right dose, Right duration and Right route.

Principle 5: *Responsible and prudent use activities involve all relevant stakeholders.*

The successful implementation of prudent use in the livestock sector requires the cooperation of all stakeholders. These include the Competent Authority and stakeholders such as the veterinary pharmaceutical industry, veterinarians, animal feed manufacturers, distributors and food animal producers, who are involved in the authorisation, production, control, importation, exportation, distribution and use of VMP containing antimicrobial agents.

Activities associated with the prudent use of antimicrobials should involve all relevant stakeholders, who all have a responsibility in this area. Part B Section II describes the roles and responsibilities of the Competent Authority, as well as industry, pharmacists, retailers and wholesalers, feed business operators, food business operators, veterinary faculties and

agricultural schools, veterinary professional associations, industry stakeholder associations and farmers' associations.

The control of AMR through prudent use of antimicrobials only if all stakeholders are well informed. Awareness campaigns therefore play a crucial role, and need to be conducted regularly and updated as necessary.

Prudent use campaigns in the livestock sector should be targeted at specific stakeholder groups in the agriculture sector, in particular farmers, veterinarians, other professionals involved in animal production. Awareness and education campaigns should include good animal husbandry practices and the appropriate use of antimicrobials. National guidelines and education programmes should promote best practices, including correct treatment, measures to prevent and reduce the transmission of pathogens, infection control and hygiene measures.

The engagement and consultation of stakeholders prior to enforcement or introduction of prudent use policies or measures are critical for successful implementation. Parties who can see the benefits (e.g. to health, trade) or understand their contribution to the control of AMR are more likely to support prudent use activities. It is therefore important for regulators to maintain a high level of communication with all stakeholder groups, as well as to the general public, such as through regular dialogue, dissemination or publication of monitoring reports, guidelines, education material and scientific publications.

Principle 6: *Prudent use of antimicrobials is part of good veterinary and good animal husbandry practice and takes into consideration disease prevention practices such as the use of vaccination and improvements in husbandry conditions*

Taking into account co-resistance and cross-resistance, any exposure to antimicrobials increases the occurrence of AMR. Therefore, to be effective in mitigating the risk of AMR, the main objective of prudent use is to bring about an overall reduction in the use of antimicrobials.

Preventing infections in the first instance is the best way to achieve this reduction and to minimise the need to use antimicrobials, as reducing the number of infections reduces the number of treatments needed. Animal diseases and infections should primarily be prevented by ensuring biosecurity, following good production and good management practices, and implementing integrated disease control programmes to minimise the occurrence of diseases and eradicate endemic disease. Measures such as discouraging health programmes in which animals are systematically treated with antimicrobials prophylactically; using scientifically proven, effective and safe alternatives to antimicrobials; using safe, high-quality feed and

water; providing incentives to farmers to encourage them to adopt effective preventive measures, will aid towards minimising disease and decreasing use of antimicrobials;

These approaches are in line with objective 3 of the Global Action Plan⁸ to “reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures” and with AMAF 38th commitment¹ to promote good husbandry practices as one of the ways to combat AMR. The principle promoted by this strategy is that prevention is better than cure. A reduction in the incidence of animal disease and zoonotic infections will minimise the need for, and use of, antimicrobials.

The objective of reducing the use of antimicrobials is also in line with animal welfare, which aims to reduce the density and production stress of the farm animal population. High stocking density is a major risk factor in the emergence and spread of infections that require the use of antimicrobials to reduce the suffering of sick animals, while production stress increases an animal’s susceptibility to disease.

The ASEAN guidelines on ASEAN Good Animal Husbandry Practices for Layers and Broilers⁵ and ASEAN Good Animal Husbandry Practices (GAHP) Animal Welfare and Environmental Sustainability Module, Layers, Broilers and Ducks⁹, also provide guidance for good husbandry practices in poultry farms.

Principle 7: *Surveillance, monitoring and the collection of reliable data provide evidence to guide policies and inform on effectiveness of measures associated with prudent use of antimicrobials in livestock.*

Surveillance and monitoring of antimicrobial resistance is necessary to provide information for carrying out risk assessment, for research purposes, evaluating antimicrobial prescribing practices, for prudent use recommendations, and the effectiveness of the measures taken to tackle antimicrobial resistance.

Surveillance data to support prudent use measures include data on¹⁰:

- antimicrobial resistance in bacteria in animals;
- antimicrobial use in food animals for infections, prophylaxis and as growth promoters;
- national import and export of bulk chemicals with potential antimicrobial use;
- levels of antimicrobial agent residues in food from animal sources.

The data could be collected using one or more of the following sources:

- antimicrobial production data from manufacturers;

- volume of antimicrobials imported by importers and exporters;
- if possible, data on intended and actual usage from manufacturers, wholesale and retail distributors including feed mills, and veterinary prescription records;
- surveys of veterinarians, farmers and producers of food-producing animals.

AMU & AMR surveillance

The collection of data on antimicrobial usage (AMU) is necessary for interpreting AMR surveillance data and can assist in responding to problems in a targeted and precise way¹¹. At the national level, AMU data collected should be analysed and published. Member States are encouraged to provide data on AMU to the OIE global database on antimicrobial use. Where possible, this should include data on usage by species and age group. Detailed surveillance and analysis of antimicrobial usage data may be able to reveal parties most commonly guilty of inappropriate usage, and why their usage is inappropriate. This would allow education programs to be more focused (and therefore cheaper and faster to implement), by targeting the party involved with a suitable and relevant message.

Regionally, a harmonised surveillance system across the region to collect comparable data on countries and animal species will allow the establishment of regional baseline data and the means to monitor trends across the region. Such data could also allow for comparison with human data. The methods used to establish such programmes (laboratory techniques, sampling, choice of veterinary antimicrobial drug(s) and microorganism(s) should be harmonised as much as possible based on international standards (e.g. OIE), but prioritised according to the regions concerns and resource constraints.

Collection of AMU data will provide important information on trends in usage in animals over time. In addition, the correlation of AMU data with AMR monitoring data will give an indication of potential association (if any) between the use of specific antimicrobials and development of resistance in bacteria from animals administered those antimicrobials¹¹.

Pharmacovigilance: Regulatory authorities should have in place a pharmacovigilance programme for the monitoring and reporting of adverse reactions to veterinary antimicrobial drugs, including lack of the expected efficacy related to microbial resistance. The information collected through the pharmacovigilance programme should form part of the comprehensive strategy to minimize microbial resistance⁷. Analysis of data collected from pharmacovigilance may also reveal situations where the conditions of use of the given veterinary antimicrobial drug should be reviewed.

Residues:

Residues are defined as all active ingredients or metabolites of those ingredients that remain in meat or other foodstuffs from the animal to which the medicinal product in question has been administered.

The monitoring of residues is usually conducted for purposes of food safety and quality assurance, to detect the presence of unacceptable levels of antimicrobial residues or prohibited drugs in animal products. However, residue monitoring can also help identify of potential risk factors associated with the inappropriate use of antimicrobials, such as illegal or excessive use of antimicrobials, failure to comply with the recommended withdrawal periods, as well as lack of proper training leading to incorrect usage.

PART B

GUIDELINES FOR PRUDENT USE OF ANTIMICROBIALS IN LIVESTOCK

General principles on the prudent use of antimicrobials should be applied as a matter of routine on farms and in veterinary practices. The following guidelines are drawn from EU's Guidelines for the prudent use of antimicrobials in veterinary medicine¹²:

SECTION I: USE & ADMINISTRATION OF ANTIMICROBIALS IN LIVESTOCK

1. Issues to be considered before using antimicrobials

Where it is necessary to use antimicrobials to safeguard animal health and welfare, the following general guidelines should be followed:

- The dispensation and administration of antimicrobials should be prescribed by a licensed veterinarian (or other suitably trained person authorised to prescribe antimicrobials in accordance with national legislation), and be justified by a veterinary diagnosis in accordance with the current scientific knowledge.
- Where it is necessary to prescribe an antimicrobial, the prescription should be based on a diagnosis made following clinical examination of the animal by the prescribing veterinarian. Where possible, antimicrobial susceptibility testing should be carried out to determine the choice of antimicrobial.
- Antimicrobial treatment must be administered to animals according to the instructions given in the veterinarian's prescription.
- When used, antimicrobials should be used as specified in the authorised product information, such as the summary of product characteristics (SPC), package leaflet and labelling, that indicates the approved use of a veterinary medicinal product.
- Off-label use should be limited to the necessary minimum and to exceptional occasions where no other authorised treatment options are available.
- The appropriate withdrawal period prior to slaughter, or for the sale of milk or eggs for human consumption must be ensured.
- Antimicrobial metaphylaxis should be prescribed only when there is a real need for treatment. In such cases, the veterinarian should justify and document the treatment on the basis of clinical findings on the development of a disease in a herd or flock. Antimicrobial metaphylaxis should never be used in place of good management practices.
- Routine prophylaxis must be avoided. Prophylaxis should be reserved for exceptional case-specific indications, where a particular disease is present on the premises or is likely to occur. The routine prophylactic use of antimicrobials should never be a

substitute for good animal health management. Prophylactic use of antimicrobials in control programmes should be regularly assessed for effectiveness and whether use can be reduced or stopped¹⁴.

- Administering medication to an entire herd or flock should be avoided whenever possible. Sick animals should be isolated and treated individually.
- All information relating to the animals: the cause and the nature of the infection and the range of available antimicrobial products must be taken into account when making a decision regarding antimicrobial treatment.
- A narrow-spectrum antimicrobial should always be the first choice unless prior susceptibility testing shows that this would be ineffective. Where appropriate, this should be supported by relevant epidemiological data. The use of broad-spectrum antimicrobials and antimicrobial combinations should be avoided (with the exception of fixed combinations contained in authorised veterinary medicinal products).
- If an animal or group of animals suffer from recurrent infection(s) requiring antimicrobial treatment, efforts should be made to eradicate the strains of the microorganisms by determining why the disease is recurring, and altering the production conditions, animal husbandry and/or management.
- Use of antimicrobial agents prone to propagate transmissible resistance should be minimised.
- The need for antimicrobial therapy should be reassessed on a regular basis to avoid unnecessary medication.
- Proper records of use of antimicrobials should be maintained. The perioperative use of antimicrobials should be minimised by using aseptic techniques.
- Wherever possible, alternative strategies for controlling disease that have been proven to be equally efficient and safe (e.g. vaccination) should be preferred over antimicrobial treatment.
- A system of pharmacovigilance should be applied to obtain information and feedback on therapeutic failures, so that potential resistance issues in the case of use of existing, new or alternative treatment options can be identified.
- A network of laboratories with the capacity for performing antimicrobial susceptibility tests in zoonotic and commensal microorganisms and target pathogens should be established in each AMS to ensure the availability of susceptibility testing.

2. Particular issues to be considered before using critically important antimicrobials

Many of the antimicrobials used in animals are also used in humans. The WHO has identified antimicrobials are critical for preventing or treating life-threatening infections in humans¹³. The European Medicines Agency (EMA) Antimicrobial Expert Group further classifies the

WHO Critically Important Antimicrobials (CIA's) based on degree of risk to humans due to antimicrobial resistance development following use in animals as follows¹⁵:

Category	Risk to Public Health	Antimicrobials Included	Advice on use
1	Low/limited risk to public health	Narrow spectrum penicillins, macrolides, tetracyclines	General principles / guidelines of responsible use to be applied
2	Higher risk to public health	Fluoroquinolones, systemic 3 rd /4 th generation cephalosporins, (aminoglycosides, broad-spectrum penicillins), colistin	Restricted to use where there are no alternatives or response to alternatives expected to be poor

Special consideration is necessary to ensure the continued efficacy of such antimicrobials and to minimise the development of resistance.

Before using these antimicrobials in animals, consideration should be given to the following (in addition to the points already mentioned):

- These antimicrobials should only be used in situations where a veterinarian has assessed, on the basis of antimicrobial susceptibility testing and relevant epidemiological data, that there is no non-critically important effective antimicrobial available.
- In exceptional cases where the use of these antimicrobials under off-label use is unavoidable and legally permissible, prescription and final use should be sufficiently justified and recorded. Such use should be based on clinical grounds, i.e. the prescribing veterinarian considers the use of a particular critically important antimicrobial necessary in order to avoid the suffering of diseased animals, and should also take into consideration ethical and public health concerns. The use of critically important antimicrobials should be limited to cases where no other alternative is available.

3. Oral administration of antimicrobials to groups of animals via feed and drinking water

Oral antimicrobial treatment is often administered to groups of animals through medicated feed or by adding the antimicrobial to drinking water or feed on the farm (e.g. top dressing).

Whenever possible, individual treatment of the affected animal(s) (e.g. injectable treatments) should be preferred to group or mass treatment. When using group treatment, the following points should be taken into account:

- Medicated feed contains a premix of veterinary medicines, and should be prescribed by a licensed veterinarian (or authorised person).
- Oral antimicrobial treatment given via medicated feed or drinking water should only be administered where prescribed by a veterinarian.
- The instructions given in the product information (e.g. SPC, leaflet, label) and by the veterinarian must be complied with, both in terms of dosage and duration of treatment.
- Off-label use should be limited to the necessary minimum and to exceptional occasions where no other authorised treatment options are available.
- Antimicrobials should only be administered to groups of animals via feed or drinking water where there is evidence of microbial disease or infection; such treatment should not be given as a prophylactic treatment. The administration of antimicrobials via feed or water should be limited to the animals requiring treatment, and the drug delivery systems should be appropriate for the intended treatment.
- The quantities of antimicrobials administered in feed or water should be monitored and documented on a continuous basis, especially in intensive food production systems.
- Where an antimicrobial is administered through feed, it is important to ensure the homogeneity of distribution of the drug, in order that each animal obtains the required therapeutic dose for treating the disease in accordance with the veterinary prescription.
- Adequate, clean storage facilities should be available on the farm to ensure proper storage of the medicated feed. Access to these facilities should be restricted.

SECTION II: RESPONSIBILITIES OF STAKEHOLDERS

Controlling AMR requires cooperation between public health, food, veterinary and environmental authorities, industry bodies, veterinarians, farmers and other parties, who all have a responsibility in this area.

1. Regulatory Authorities

The Regulatory Authorities at local and national levels are responsible for pursuing a proactive approach to developing appropriate risk-based measures to ensure the prudent use of antimicrobials, verifying and enforcing their application, and evaluating the results. They are also responsible for providing sufficient resources for implementing these measures and for research and awareness campaigns. Regulatory authorities are also responsible for marketing authorisation, to ensure the safety, quality and efficacy of veterinary products, including antimicrobials for livestock use.

The Regulatory Authority should:

- ensure that national strategies are developed and implemented. Such strategies should be based on cooperation between the veterinary authorities, the human health authorities and other relevant authorities (e.g. environmental authorities);
- monitor the implementation of the national strategy, in order to evaluate and assess the impact and effectiveness of measures taken under it;
- Ensure an effective registration system for antimicrobial products is in place;
- carry out, where appropriate, targeted checks on veterinarians with high levels or concerning patterns of prescription. Obligatory educational courses may be considered for veterinarians with questionable prescribing practices. Farm inspections should also be carried out in order to evaluate animal husbandry and animal health conditions;
- consider the introduction of mandatory herd health programmes promoting best practices, and ensure that hygiene standards are improved on farms where problems have been identified;
- support and promote research into alternatives to antimicrobials, diagnostic tests and the prudent use of antimicrobials;
- support the development, dissemination and implementation of guidelines for both the prudent use of antimicrobials and hygiene measures; support awareness and training campaigns on AMR and the prudent use of antimicrobials aimed at farmers and veterinarians;
- develop control measures to limit the spread of resistant bacteria when a type of AMR is low or emerging. This may include increased biosecurity measures, identification of carriers, animal quarantine, restrictions on the movement of people and investigations;

- set up surveillance programmes on antimicrobial usage and resistance, and for monitoring their implementation;
- conduct risk assessments on the use of antimicrobials in livestock.

2. Prescriber (Veterinarian or Authorised Person)

The prescriber of the antimicrobial should be a veterinarian (or other suitably trained person authorised to prescribe antimicrobials in accordance with national legislation) who is familiar with the history of the herd, flock or animal being treated.

It is necessary to ensure that the prescriber can make the treatment decision in an independent way, so as to avoid a conflict of interest. The relation of the prescriber to the farmer should therefore be one that ensures independent decisions, and is one primarily based on expert knowledge.

This can be achieved in a number of different ways:

- by introducing measures to limit financial incentives between veterinary practitioners, suppliers of antimicrobials and the pharmaceutical industry, and to restrict potential conflicts of interest that could facilitate the inappropriate or unnecessary prescription and sale of antimicrobials, whilst still allowing for balanced systems of veterinary health care;
- by putting in place contracts or arrangements between the farmer and a veterinarian for a specific herd or flock, such that the veterinarian can develop a better understanding of the overall health status of the herd or flock, and thereby reduce the prevalence of disease and the use of antimicrobials.
- Where it is necessary to prescribe an antimicrobial, the prescribing veterinarian should ascertain himself by means of an on-site clinical examination that the symptoms indicate a bacterial infection.
- Whenever possible, the prescriber should take appropriate samples from which he/she can identify the pathogen and measure its antimicrobial susceptibility. In acute cases, when treatment needs to be started immediately to avoid animal suffering or to limit the spread of infection, it is still advisable to collect samples. If samples are collected immediately prior to the start of treatment, susceptibility testing can be carried out whilst treatment is being given. The results of this can then be used to validate the choice of antimicrobial and to inform epidemiological follow-up. Where treatment is being given on an ongoing basis, repeated culture and sensitivity testing allows antimicrobial sensitivity trends to be monitored, and the treatment revised subsequently if necessary.

The prescriber should follow national and/or international recommendations for prescribing and administering antimicrobials. Attention should be given to:

- up-to-date treatment guidelines provided by national authorities or veterinary professional bodies to assist veterinarians in selecting the appropriate antimicrobial and fixing a suitable dosing regime and route of administration;
- practice-based protocols for common infections, which take into account regional and local trends in antimicrobial sensitivity. These can help veterinarians to make optimal prescribing decisions in the absence of susceptibility data. Timely publication and availability of up-to-date national surveillance data facilitates the development of local protocols.
- The prescriber should ensure that the most appropriate antimicrobial is selected, based on the most accurate and up-to-date information on pharmacodynamics and pharmacokinetics and on accurate and up-to-date information on the functioning of the different classes of antimicrobials.
- The prescriber should always consider using single substances instead of combinations of antimicrobials and should ensure that, where a combination of antimicrobials is prescribed, all the substances in the combination are active against the target pathogen(s).
- The prescriber is responsible for providing correct information to the person administering the antimicrobial. This should be based, in the first instance, on the information from the product information relating to the dose, the indications, the withdrawal periods and prudent use warnings.

Veterinarians should report the lack or reduced efficacy of an antimicrobial product to the authorities without delay. Reporting should be carried out within the existing pharmacovigilance system.

In view of the risk of AMR, the prescriber should always give consideration to alternative solutions, in both the short and long terms, which could prevent recurrence of the disease.

3. Administrator of the antimicrobial (Farmer or Farm Personnel)

The person administering antimicrobials to food-producing and aquaculture animals is often the farmer or staff working on the farm. They are responsible for closely following the prescriber's instructions on administering the antimicrobials. They also play a critical role in monitoring sick animals and animals that do not need antimicrobials. Farmers who use good quality feed and appropriate feed management and biosecurity measures can influence their animals' health for the better and reduce the potential need for antimicrobials.

The person administering antimicrobials should:

- obtain the antimicrobials from authorised sources, based on a veterinary prescription;
- cooperate with the veterinarian who regularly visits the animals and knows the history and current health status of the herd, flock or animal, to allow him/her to put in place disease prevention measures that also take account of animal welfare;
- always follow the prescriber's instructions, the product information on the product and government guidelines (or guidelines from other organisations) on administering antimicrobials prudently, especially when treating animals with oral medication (antimicrobials added to feed or water);
- to ensure the safety of the food production chain, he/she must ensure that the recommended withdrawal periods are observed, to avoid residues of antimicrobials appearing in meat, milk or other products.
- when administering antimicrobials to a group of animals, farmers or any other person administering antimicrobials, should ensure that the correct group of animals is treated, at the required dosage, and for the specified duration of the treatment;
- be aware of the general aspects of prudent use of antimicrobials and AMR, including the need to take samples and perform antimicrobial susceptibility testing on target pathogens.

The appetites of diseased animals can be depressed, so farmers or any other person administering antimicrobials should monitor whether all animals ingest the adequate/full quantity of the medicated feed containing the therapeutic dose, to avoid under-dosing. Where there is a risk of these occurring, the farmer should inform the prescribing veterinarian who should assess the need to modify the treatment regime (e.g. by switching to parenteral treatment).

4. Pharmaceutical industry, pharmacists, retailers and wholesalers

Prudent use measure includes veterinary prescription for dispensing veterinary medicinal products for food-producing animals. The advertising to the general public of veterinary medicinal products that require veterinary prescription should be prevented.

Stakeholders who supply antimicrobials to the end-user, such as pharmacists and retailers, are responsible for ensuring that a valid prescription is presented at the time antimicrobials are supplied, including in the case of internet sales, and for providing clear and correct information on product use.

The pharmaceutical industry and wholesalers should limit their advertising to veterinarians to objective information, which is in line with approved SPC. The information provided should also highlight the risk of AMR and the need for prudent use. Promotional campaigns involving

economic or material benefits for prescribers or suppliers of veterinary medicines should be avoided.

The pack size and the strength of the available antimicrobial formulations should be adapted as far as possible to the approved indications of use, so as to avoid, for example, improper dosing and overuse. In addition, the pharmaceutical industry, wholesalers and those involved in the sale of antimicrobials should cooperate to implement measures to monitor and control the supply and use of antimicrobials, such as providing information on veterinary sales and the results from industry monitoring programmes to competent authorities.

The pharmaceutical industry is encouraged to prioritise and focus on developing and marketing alternatives to antimicrobials, such as vaccines and rapid and affordable diagnostic tests. Pharmaceutical industry should also prioritise tasks like dose optimisation (based on relevant pharmacokinetic and pharmacodynamic data), modern formulations of old classes of antibiotics such as penicillins (which are still effective against many animal diseases) and antimicrobials for minor use/ minor species. The development of fixed combinations of veterinary antimicrobials should be avoided unless adequately justified.

5. Feed business operators

Feed business operators must comply with the legal requirements for feed hygiene, implement best practices in the production of safe and nutritionally balanced feed, and ensure adequate feed formulation. They must also ensure that all ingredients meet the required standards and that the manufacturing process does not allow the feed to be contaminated with deleterious agents, which could compromise the safety of the feed.

Feed businesses operators producing medicated feed must be approved for the manufacture of medicated feed and follow all legal requirements for medicated feeds. They should only produce medicated feed from authorised veterinary medicinal products and in accordance with a veterinarian's prescription. They should follow good manufacturing practices and ensure appropriate mixing to guarantee the homogeneity of antimicrobials in the feed. They must take steps to avoid cross-contamination and minimise the transfer of antimicrobials to subsequent batches of feed.

Medicated feed should be appropriately labelled and only be supplied to the end-user on presentation of a valid veterinary prescription. Detailed records should be kept of the antimicrobials used, the medicated feed produced and the destination.

6. Food business operators

Food business operators, including retailers, should favour food produced in accordance with quality schemes and systems of production and supply that apply the principles of prudent use, i.e. that minimise the use of antimicrobials and promote high standards of animal welfare. They should not make claims that could confuse or mislead consumers (e.g. ‘antibiotic-free’) when marketing meat and other products from animals reared under ‘prudent use’ conditions (as antibiotics can be used legally in accordance with SPC indications). Consumer organisations should proactively support such initiatives.

7. Veterinary faculties and agricultural schools

Veterinary faculties and agricultural schools or colleges should ensure that sufficient attention is given to the problem of AMR and the prudent use of antimicrobials in their undergraduate and post-graduate programmes, and that knowledge relating to these areas is kept up to date. Under- and post-graduate programmes should also focus on developing learning materials and techniques relating to ways to improve and promote breeding and husbandry practices that promote animal health. Such practices may include biosecurity measures, good farming practices and herd health planning that prevent infections and therefore reduce the need for antimicrobials.

Providing information on antimicrobials and AMR should even be considered in basic education on public health and food safety, e.g. in secondary schools. Universities and other research facilities should give priority to research in the area of AMR, with focus on:

- developing alternative, preferably preventive, tools for infection control;
- evaluating the impact of the use of antimicrobials in animals on public health and the environment;
- further investigating pharmacokinetic and pharmacodynamic data and using models to simulate the effects of different dosing schedules (based on different combinations of: disease, pathogen, target tissue and animal species). The results from modelling should provide a scientific background for setting effective dosing schedules in practice;
- further investigating co-resistance and cross-resistance, including the co-resistance of disinfectants and antimicrobials and the co-resistance and development of resistance of antimicrobials to certain metals;
- developing new classes of antimicrobials;
- Veterinary faculties should provide information on the risk of nosocomial infections in veterinary practices and clinics, on the use of monitoring procedures to detect and

report occurrence of infections and on the use of infection prevention and control measures to minimise occurrence;

- promoting the principles of prudent use in scientific publications.

8. Veterinary statutory bodies and professional associations

Veterinary professional associations should continue developing guidelines for the prudent use of antimicrobials and promoting their implementation. Veterinary professional associations and statutory bodies engaged in the licensing of veterinarians should provide specific training for veterinary practitioners on AMR and the prudent use of antimicrobials, as a core component of continuing professional education. They should include principles on the prudent use of antimicrobials in their codes of conduct for veterinarians.

9. Industry stakeholder associations

Industry stakeholder associations should continue to support the development and implementation of initiatives to tackle AMR and to promote the prudent use of antimicrobials. They should develop appropriate communication materials and provide adequate information about the risk of AMR to their members. They should also support national initiatives involving the collection of data on sales of antimicrobials. Industry stakeholder associations should promote quality schemes and systems of production and supply that implement the principles of prudent use, i.e. that minimise the use of antimicrobials and promote animal welfare.

10. Farmers' associations

Farmers' associations should promote the principles of prudent use of antimicrobials among their members. They should inform farmers of the implications of the use of antimicrobials in animals for the risk of AMR, and thus help to minimise the use. Other aspects such as the risk of AMR due to direct contact with animals should also be publicised. Training courses and guidance materials given to farmers should include information on preventive measures that promote animal health, in particular implementation of biosecurity measures, good farming practices and herd health planning. Such practices can help to reduce the need for antimicrobials. Training should also cover the administration of antimicrobials and environmental risks.

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Annex 1: Glossary

Antimicrobial agent- Any substance of natural, synthetic or semi-synthetic origin which at low concentrations kills or inhibits the growth of micro-organisms but causes little or no host damage.

Antimicrobial class - Antimicrobials with a related molecular structure, often with a similar mode of action. Variations in the properties of antimicrobials within a class often arise as a result of the presence of different side chains of the molecule, which confer different patterns of pharmacokinetic and pharmacodynamic behaviour on the molecule.

Antimicrobial growth promoter - Antimicrobial agents used for the purpose of increasing daily weight gain or feed efficiency (feed-weight gain ratio) of food-producing animals.

Antimicrobial metaphylaxis – the timely mass medication of a group of animals to eliminate or minimise an expected outbreak of disease.

Antimicrobial resistance - The ability of a micro-organism to resist the effects of an antimicrobial agent. This can occur by mutation or by acquisition of a resistance gene from other microorganisms.

Livestock (in context of ASWGL) - Domestic animals raised for the purpose of providing food for humans, such as poultry, pig, cattle, buffalo, goats.

Off-label use or “extra-label use” - any use of an approved drug that differs from instructions on the approved product label.

Pharmacokinetics The ways in which antimicrobials (principally drugs/medicines) are absorbed by, move within, and are finally eliminated from animals, humans, etc.

Pharmacodynamics The behaviour (e.g. quick, slow, short term, long term, etc.) of an antimicrobial at its receptor site (i.e. where it initiates its effect

Prophylaxis - The administration of an antimicrobial to healthy animals prior to an expected exposure to an infectious agent or, following such an exposure prior to onset of laboratory-confirmed clinical disease. In general, such usage is in a herd or flock situation and not an individual animal.

Registration (Licensing, Authorization, Approval)- The process of approving a drug for marketing in a country/region. Includes assessment using particularly the criteria of safety, quality and efficacy.