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European regulations on the use of antibiotics in veterinary medicine

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ABSTRACT

Antimicrobial resistance endangers the successful combat of bacterial infections in humans and animals. The common use of antibiotic classes including those of high clinical value in human as well as veterinary medicine is a critical factor contributing to or suspected to promote the emergence of antibiotic resistance. New legal provisions laid down in veterinary drug legislations and related guidelines and advice are in force in the European Union to safeguard the effectiveness, accessibility and availability of antibiotics.

Categorisation of antibiotics in classes of importance for treatment of infections of humans by the WHO was one of the first steps. This task is also undertaken for antibiotics for treatment of animals by the EMA's Antimicrobial Advice Ad Hoc Expert Group. The new veterinary Regulation (EU) 2019/6 has extended restrictions for use of some antibiotics in animals to a full ban of certain antibiotics. While some (but not all) antibiotic compounds not being authorized in veterinary medicine may still be used in companion animals more strict provisions were already applicable for treatment of food producing animal species. Distinct regulations are in place for the treatment of animals kept in large numbers in flocks. Initial regulations focussed on the protection of consumers from residues of veterinary drugs in food commodities, new regulations address prudent (not routinely) and responsible selection, prescription and use of antibiotics, and have improved the practicality for cascade use outside the terms of marketing authorisation. Mandatory recording of use of veterinary medicinal products for food safety reasons is extended to rules for veterinarians and owners or holders of animals to regularly report the use of antibiotics for the purpose of official surveillance of consumption. National sales data of antibiotic veterinary medicinal products have been collected on a voluntary basis until 2022 by ESVAC, which has created awareness of major differences between EU member states. A significant decline in sales was reported for third and fourth generation cephalosporines, polymyxins (colistin), and (fluoro)quinolones since the initiation in 2011.

1. Introduction

In the European Union (EU), the regulatory framework for getting a marketing authorisation for a veterinary medicinal product (VMP) is similar to that for human medicines. For both medical disciplines the so called centralised, decentralised, mutual recognition and national procedures are in place and can be used (EU 2019/6, 2019). But also significant differences in medicines management exist between the human and veterinary field. Among these differences are the size of industry and market, and – most obvious – the therapeutic target groups, the latter being most heterogeneous in biological, medical, and husbandry techniques on the veterinary side. In veterinary medicine, the major subdivision is companion animals such as dogs, cats etc. versus so called food producing species comprising big (cattle) and small (sheep, goat) ruminants, pigs, equids, fish and so forth. These animals may be kept individually, in groups or large herds.

Special rules exist for owners or keepers of animals of the equine species. The operators are obliged to verify in a lifetime document those individual animals not being intended for slaughter for humans (Reg. (EU) 2016/429, Art. 114 (1)). This implies that such horses can be

Abbreviations: AMEG, EMA Antimicrobial Advice Ad Hoc Expert Group; AMU, Antimicrobial Medicines Use; ESVAC, European Surveillance of Veterinary Antimicrobial Consumption; MRL, Maximum Residue Limit; SPC, Summary of Product Characteristics; VMP, Veterinary Medicinal Product; WHO, World Health Organisation; WOAH, World Organisation for Animal Health.

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treated with medicines allowed for any companion animals.

Although not discussed in detail herein it is worth to mention that on the other hand "food producing" horses can be treated with "Essential Substances" listed in Regulation (EC) No 1950/2006 as amended by Commission Regulation (EU) No 122/2013 in addition to substances anyway allowed for food producing animals (Commission Regulation (EU) 122/2013).

As a consequence, the need for medicinal products is very specific, depending on the medical requirements of the animal species, the diagnosis, age, and type of husbandry. Eventually, all animals may require antimicrobial treatments for infections caused by pathogens, some of which are species-specific and others causing disease across different species. In the following sections, the focus will be on the classification system developed by EMA with the contribution of an Antimicrobial Advice ad hoc Expert Group (AMEG). The focus will be farm animals, in most countries these animals will have the largest part of veterinary antimicrobial use.

Use of antimicrobials should be addressed in the context of One Health Concept of the World Health Organisation (WHO). This concept outlines "an integrated, unifying approach to balance and optimize the health of people, animals and the environment." One Health "involves the public health, veterinary, public health and environmental sectors." As such it converges human, animal and environmental health (WHO, 2017). The EMA antimicrobial classification system and Regulation EU 2019/6 referred to herein serve to achieve these objectives (Reg. (EU) 2019/6, Recital 41), thereby emphasizing the prudent use of antimicrobials in veterinary medicine. An example of comparable legislation in human medicine is Regulation (EU) 2022/2371, addressing monitoring, early warning of, and combating serious cross-border threats to health, and that Member States are, in liaison with the Commission, to coordinate among themselves their policies and programmes in the areas covered by Union action in the field of public health (Regulation (EU) 2022/2371, 2022).

2. Antibiotic classes/substances for use in food producing species, companion animals and in human medicine

All antibiotic classes shown in Table 1 are authorized for treatment of food producing species, most also authorised for companion animals. All of these classes (although not all individual substances) are also used in human medicine. In exceptional cases, e.g. when a specific route of administration like intravenously is needed or with specific pathogens, companion animals can also be treated with medicinal products licensed for use in humans (see sections 2.1 and 2.2), preferably after antimicrobial testing.

The most critical consequence of the common use of antimicrobial substances is seen in the selection and spreading of bacteria with co- or cross-resistance to antibiotics used in human medicine. To target the emergence of antimicrobial resistance several strategies to classify antibiotics have been issued, e.g., by the WHO with focus on human medicine and the World Organisation for Animal Health (WOAH, formerly OIE) and by the European Medicines Agency (EMA) with focus on treatment of animals (World Health Organisation, 2019; WOAH, 2021; Watts et al., 2020; EMA, 2020). Next section will focus on the veterinary antibiotics classification system developed by EMA's Antimicrobial Advice ad hoc Expert Group (AMEG) (EMA, 2020).

2.1. EMA Categorisation of antibiotics for use in animals

The EMA categorisation of antibiotics for use in animals for prudent and responsible use addresses two major criteria: i) the potential risk of veterinary antibiotics to increase the development of resistance in regard to public health and ii) consideration of the value of the given antibiotic in veterinary medicine. At the same time EMA explicitly recognizes the value of national guidelines on use of antibiotics that should be continued. Additionally, provisions given in the Summary of Product

Table 1
Antibiotic classes for use in the EU in (food producing) animal species and in human medicines. Not all individual compounds listed are licensed for use in human.

Antibiotic class/substance*	EMA Classification	Target food producing animal species and indication**
Cephalosporins, 3rd- and 4th-generation with exception of combinations with beta-lactamase-inhibitors (Cephalosporins, 3rd, 4th and 5th generation***)	B	All mammalian food producing species (compound and species-specific provisions). Treatment of disease (pneumonia) associated with *Pasteurella trehalosi* (former *P. haemolytica* serovar T), *Mannheimia haemolytica* (former *P. haemolytica* biogroup I) and *Pasteurella multocida*.
Polymyxines (Colistin, polymyxin B)	B	Bovine, ovine, porcine, chicken, rabbits Prevention and treatment of diseases caused by sensitive bacteria (e.g., Salmonella and *Escherichia coli*).
Quinolones: fluoro and other quinolones (Danofloxacin, enrofloxacin, flumequine, marbofloxacin; ibafloxacin, pradofloxacin only companion animals)***	B	All food producing species (compound and species-specific provisions) First. gen., oxolinic acid, flumequine: Treatment of septicaemias, infections (colibacillosis) Second Gen.: cinoxacin, danofloxacin, difloxacin, enrofloxacin. Wide range of applications, extremely important, treatment of septicaemias, respiratory and enteric diseases.
Amphenicols (Florfenicol, thiamphenicol; chloramphenicol is banned for use in food animals)	C	All food producing species (compound and species-specific-provisions) Extremely important (wide range of applications and the nature of the diseases treated). Particular importance in treating some fish diseases (no or very few treatment alternatives). Useful alternative in respiratory infections of cattle, swine and poultry. Florfenicol is used to treat pasteurellosis in cattle and pigs.
Pleuromutilins (Tiamulin, valnemulin)	C	Porcine, rabbit, chicken, turkey (compound- and species-specific provisions) Treatment and prophylaxis of dysentery, pneumonia and mycoplasmal infections in pigs and poultry; swine dysentery (*Brachyspira hyodysenteriae*).
Lincosamides (Clindamycin (companion animals only), lincomycin, pirlimycin)	C	All food producing species (compound- and species-specific provisions) Mastitis pathogens, mostly Gram-positive bacteria such as Staphylococci (e.g., *Staphylococcus aureus*) and Streptococci (*Streptococcus agalactiae, S. uberis, S. dysgalactiae*).

(*continued on next page*)

Table 1 (*continued*)

Antibiotic class/substance*	EMA Classification	Target food producing animal species and indication**
Cephalosporins, 1st- and 2nd-generation, and cephamycins (Cefacetrile, cefadroxil (companion animals only), cefalexin) Penicillins with beta-lactamase inhibitor (amoxicillin/clavulanic acid)	C	Cattle, sheep, pig (compound- and species-specific provisions); cefalexin-sensitive infections; bovine: intramammary treatment of mastitis in lactating
Macrolides and ketolides (Erythromycin, gamithromycin, tulathromycin, tylosin, tylvalosin)***	C	All food producing species (compound- and species-specific provisions) Mycoplasma infections (pigs, poultry), haemorrhagic digestive disease in pigs (*Lawsonia intracellularis*) *Fusobacterium necrophorum*) in cattle, where they have very few alternatives. Respiratory infections in cattle.
Aminoglycosides (except spectinomycin) (e.g. streptomycin, gentamicin)	C	Aminoglycosides are very critically important antimicrobials in veterinary medicine and one of few treatment options presenting a lesser risk for Pseudomonas infections in companion animals and horses and weaning diarrhoea due to Enterobacterales in pigs.
Penicillins (Aminopenicillins without beta-lactamase inhibitors; natural, narrow-spectrum penicillins (beta-lactamase-sensitive penicillins), anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)	D	All food producing species (compound- and species-specific provisions) For example: used in pigs for treatment and control of *Streptococcal meningitis* and septicaemia caused by *Streptococcus suis*, and for treatment and control of pleuropneumonia caused by *Actinobacillus pleuropneumoniae* and of secondary pneumonia caused by *Pasteurella multocida* Penicillins are used in the treatment of septicaemias, respiratory and urinary tract infections.
Sulfonamides, dihydrofolate reductase inhibitors and combinations (Formosulfathiazole, sulfadiazine, sulfadoxine, trimethoprim)	D	All food producing species (species- and compound-specific provisions) Extremely important; wide range of applications and the nature of the diseases; bacterial, coccidial and protozoal infections; wide range of animal species.
Tetracyclines	D	All food producing species (species- and compound-specific provisions) Very important in the treatment of many bacterial and chlamydial diseases in a broad range of animal species. No alternatives in the treatment against heartwater (*Ehrlichia ruminantium*) and anaplasmosis (*Anaplasma marginale*).
Aminoglycosides: Spectinomycin only	D	All food producing species (compound and species-specific limitations) Used for respiratory infections in cattle and enteric infections in multiple species.

* Enumeration and classification according to EMA (EMA, 2020). Antimicrobial classes of Category A are not licensed for use in veterinary medicine in the EU and not mentioned in this table. Antibiotic classes solely for use in companion animal species are not listed.

** Indications and target animal species are exemplarily specified and not listed exhaustively.

*** Classified by WHO as Highest Priority Critically Important Antimicrobials for human use (World Health Organisation, 2019). Compound and species-specific provisions: Not all compounds of an antimicrobial class may be allowed for use in the food producing species indicated; also, there may be specific provisions for products derived from treated animals, e.g., milk, eggs.

Characteristics (SPC), in regional guidelines on the use in food producing animal species as well as in other professional information including national prescription policies remain valid (EMA, 2020).

EMA classifies antibiotics in 4 different categories designated as

Table 2
Antibiotics not authorized for use in veterinary medicinal products in the EU. Category A antibiotics are not allowed for use in food producing animals. Antibiotics listed in the annex of Commission Implementation Regulation are banned from use in any animal species.

Antibiotic Class	Examples of EMA Category A substances	Registration in the Annex of Commission Implementation Regulation (EU) 2022/1255
Aminopenicillins*	Mecillinam, pivmecillinam	yes
Carbopenems	Merpenem, doripenem	yes
Carboxypenicillin and ureidopenicillin, including combinations with beta lactamase-inhibitors	Piperacillin-tazobactam	yes
Glycopeptides	Vancomycin	yes
Cyclocyclines	Tigecyclin	yes
Ketolides	Thelithromycin	no
Lipopeptides	Daptomycin	no
Monobactams	Aztreonam	yes
Oxyzolidinones	Linezolid	yes
Phosphonic acid derivatives	Fosfomycin	yes
Pseudomnic acids	Mupirocin	no
Rifamycins (except rifaximin)**	Rifampicin	no
Riminofenazines	Clofazimine	no
Sulfones	Dapson	no
Streptogramins	Pristinamycin, virginiamycin	no
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Isoniazid, ethambutol	no
Other cephalosporins and penems (ATC code JO1D1), including combinations of 3rd-generation cephalosporins with beta lactamase-inhibitors	Ceftobiprole, ceftaproline	yes
Substances newly authorized in human medicine following publication of the AMEG categorisation	To be determined	-

* For veterinary aminopenicillins see Tab. 1

** Rifaximine is authorized in VMPs for intramammary application in dry cows.

Category A, B, C, and D (EMA, 2020) and all 4 categories are applicable for food producing animal species as well as companion animals.

Antibiotics listed in Category A (Avoid) are not licensed for use in any animal species in the EU. However, it must be noted that such antimicrobials can be used for treatment of companion animals in exceptional cases, e.g., in cases of a therapeutic gap (Reg. (EU) 2019/6 Article 112) (Table 1), except for some substances (Reg. (EU) 2019/6 Article 37).

Some antibiotics, although categorized, are not allowed to be used in food producing animal species. For chloramphenicol, dapsone, dimetridazole, metronidazole, the nitrofurans, and ronidazole it was not possible to establish a Maximum Residue Limit (MRL) in food stuffs of animal origin in accordance to Commission Regulation No 37/2010; they are listed in Table 2 of this Regulation as prohibited substances for food-producing animals (Reg. (EU) 37/2010, 2010).

2.2. Antibiotics for use in animals or reserved for human use

EMA Category A antimicrobials include rifamycins (except rifaximin), streptogramins, ketolides and drugs used solely to treat tuberculosis or other mycobacterial diseases and these active substances are not automatically included in the list of antimicrobials reserved for human use (Table 2).

In EU 2019/6, Article 37 (5) is stated that "the Commission shall, by means of implementing acts, designate antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans." The criteria for limitation of antimicrobials to exclusive use in humans include high importance to human health, risk of transmission of resistance, and non-essential need for animal health and are depicted in Delegated Regulation (EU) 2021/1760 (Commission Del. Regulation (EU) 2021/1760, 2021) (Table. 2).

These criteria led to Implementing Regulation (EU) 2022/1255, in force from 9 February 2023, which designates 18 antimicrobials (groups or compounds) that are not allowed to be used in animals and as a consequence cannot be used in accordance with Articles 112, 113 and 114 (Commission Impl. Regulation EU 2022/1255, 2022) (see 3.2).

In conclusion, while some compounds in Category A can be used in exceptional situations outside the terms of the (human) marketing authorization in companion animals, substances listed in the Annex of (EU) 2022/1255 are reserved for treatment of certain infections in humans and are prohibited for use in any animal.

Category B (Restrict) antibiotics are compounds listed under "Critically Important Antimicrobials (CIA)" by the WHO, i.e., compounds of particularly high value in human medicine. Only compounds meeting both criteria "Sole, or one of limited available therapies, to treat serious bacterial infections in people" and "Used to treat infections caused by bacteria possibly transmitted from non-human sources, or with resistance genes from non-human sources" are designated as CIA (World Health Organisation, 2019).

In veterinary medicine, such antimicrobials should be used "only when there are no antibiotics in Categories C or D that could be clinically effective". Their "use should be based on antimicrobial susceptibility testing, where possible" (EMA, 2020) (Table 1).

Category C (Caution) comprises antibiotics for which there are no alternatives in human medicine and no clinically effective alternatives in Category D for veterinary medicine. For instance, no alternatives are available for pleuromutilins (e.g., valnemulin) for the treatment of intestinal brachyspirosis in pigs in Category D. In conclusion, Category C antibiotics should only be taken into consideration when there are no potentially effective alternatives in Category D.

Finally, Category D (Prudence) antibiotics "should be used as first-line treatments whenever possible. They should be used prudently and, as always, should be used only when medically needed".

For antibiotics listed in Category D as well as in the other categories it is self-evident that they may not be used unnecessarily, not for overly long treatment periods and should not be underdosed. Detailed rules applying to prudent use can also be found in Commission Notice 2015/C 299/04 (2015).

3. Rules to diminish emergence and spread of antimicrobial resistance and for preserving public health

On 28 January 2022, Regulation (EU) 2019/6 came into force. Seen as a whole, the new Regulation "lays down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of veterinary medicinal products" (Reg EU 2019/6, 2019, Article 1). The aim is to set "high standards of quality, safety and efficacy for veterinary medicinal products (VMPs) in order to meet common concerns as regards the protection of public and animal health and of the environment." As stated above, many modern antibiotic classes or compounds of high clinical value in human as well as in veterinary medicine share respective marketing authorisations and are in use for the treatment of humans and animals. The classification systems of antibiotics according to their clinical importance is essential to preserve major aspects of public health but not necessarily sufficient to diminish the risks inherently linked to their use in daily practice and to prevent emergence of antimicrobial resistance. In line with the One-Health-Approach EU 2019/6 does serve this objective with specific rules and guidance on use, management and monitoring of sales and use of antimicrobial (V)MPs.

3.1. Rules for prescription of antimicrobial medicinal products and limitations of use

A veterinary practitioner is allowed to administer an antibiotic medicinal product in several clinical situations: as a therapeutical intervention and exceptionally for prophylaxis or metaphylaxis, for individual animals or a group of animals. In any case, the application must be justified and is preceded by clinical examination or another "proper assessment of the health status", e.g., based on an evident epidemiological situation and whenever possible identification and sensitivity testing of the pathogen (Reg. (EU) 2019/6, Article 105).

Antimicrobial medicinal products may not be administered for routine prophylaxis, i.e., "the administration of a medicinal product to animals or a group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection" (Article 105). Antimicrobial products may only be applied for prevention in exceptional cases and only to individual animals or a restricted number of animals for diminishing the consequences of an infection when severe consequences are to be expected.

Analogous rules apply for metaphylactic treatments. In veterinary medicine, metaphylaxis is defined as the administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected (Article 4 (16), Article 107). Antimicrobials may be used only in situations "when the risk of spread of an infection or of an infectious disease in the group of animals is high and where no appropriate alternatives are available".

The prescriptions should include the name of the prescribed medicinal product, including its active substances, pharmaceutical form and strength, quantity prescribed, dosage regimen; and for food-producing animal species, withdrawal period even if such period is zero (Article 105).

Antimicrobial medicinal products "shall not be used in animals for the purpose of promoting growth nor to increase yield" (Article 106). The last antimicrobial growth enhancer in the EU was banned from 2006 onwards (Reg. (EC) No 1831/2003, 2003, Article 11).

The universal rules for use of antimicrobial medicinal products are listed in Article 107: "VMPs shall be used in accordance with the terms of the marketing authorization, no routine use, no use to compensate for

poor hygiene, inadequate animal husbandry or lack of care or poor farm management, no use for the purpose of promoting growth or to increase yield, limited use for prophylaxis or metaphylaxis" and "no use of antibiotics reserved for treatment of certain infections in humans (…)" is accepted.

Prescription of antimicrobials categorized in Category B (and A) of EMA should be based on antimicrobial susceptibility testing, where possible" (EMA, 2020). Some countries, like for instance the Netherlands (Ministry of Health, Welfare and Sport, The Netherlands), Belgium (Belgisch Staatsblad, 2016) and Denmark (MFAF Denmark), have national legislation in place that demands susceptibility testing to verify that no other antibiotics belonging to less important groups will be effective, before an antimicrobial belonging to fluoroquinolones or $3^{rd}/4^{th}$ generation cephalosporins can be prescribed. This was implemented in 2014 in the Netherlands, and since 2011 substantial reductions in prescription of fluoroquinolones (-92%) and $3^{rd}/4^{th}$ generation cephalosporins (-99%) were realized.

3.2. Use of medicines in animals outside the terms of marketing authorisation

Special rules apply for situations when there is no indicated antimicrobial (or any other VMP) authorized or available for the animals under care of the responsible veterinarian in the respective Member State. In such cases, use outside the terms of marketing authorization is possible and the responsible veterinarian may select – under direct personal responsibility - an alternative medicine for a non-food producing animal in the following order (referred to as "cascade") (Dir. 2001/83/EC, 2001; Reg. (EC) No 726/2004, 2004; EU 2019/6, 2019, Articles 112, 113, 114, 115):

"(a) a veterinary medicinal product authorised under this Regulation in the relevant Member State or in another Member State for use in the same species or another animal species for the same indication or for another indication;

(b) if there is no veterinary medicinal product as referred to in point (a) of this paragraph, a medicinal product for human use authorised in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004;

(c) if there is no medicinal product as referred to in point (a) or (b) of this paragraph, a veterinary medicinal product prepared extemporaneously in accordance with the terms of a veterinary prescription".

Use of antibiotics reserved for treatment of certain infections in humans is prohibited in steps (b) and (c).

Comparable explicit rules exist for food producing animals specified for terrestrial and aquatic species. Again, specific "cascades" for choosing an appropriate medicine must be applied, in consideration with available MRL's (Reg. (EU) 37/2010, 2010). In any case, the veterinarian is responsible for the use of the antimicrobial, but also to avoid unacceptable suffering in the animal. The veterinarian may also allow another person (e.g., farmer, animal owner) to administer the cascade medicinal product under his/her responsibility and in accordance with national provisions.

3.3. Withdrawal Periods

The Summary of Product Characteristics (SPC) (as well as the package insert) of each VMP for a food producing animal species specifies the target animal species, indication, dosing regimen, route of administration and the withdrawal period. The withdrawal period means "the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health" (Reg. (EU) 2019/6, 2019, recital 25, 34). Per active substance and food commodity (e.g., meat, milk, egg), the determination of withdrawal periods depends on animal species, route of administration, VMP formulation and dosing scheme, and are VMP specific (not generic!).

When a veterinary medicinal product is used within the terms of the SPC, the length of the specified withdrawal period has to be complied with.

In case of (antimicrobial) medicines administered outside the terms listed on the SPC the withdrawal periods listed in the SPC are not appropriate, or if the product is authorized for companion animals or human use or prepared extemporaneously, the withdrawal period is even unavailable. In order to protect the consumer of residues in foodstuffs appropriate withdrawal periods have to be issued by the responsible veterinarian. In contrast to previous legislation, in Regulation (EU) 2019/6 (2019), obligatory rules for determination of the appropriate withdrawal period for food-producing animal species have been defined and are given here below; in general available withdrawal periods should be multiplied with the factor 1.5 (Reg. (EU) 2019/6, 2019, Article 115) e.g.:

"1.(a) For meat and offal from food-producing mammals and poultry and farmed game birds the withdrawal period shall not be less than:

"i) the longest withdrawal period provided in its summary of the product characteristics for meat and offal multiplied by factor 1.5; ii) 28 days if the medicinal product is not authorised for food-producing animals; iii) one day, if the medicinal product has a zero withdrawal period and is used in a different taxonomic family than the target species authorised.

2. If the calculation of the withdrawal period according to points (a)(i), (b)(i), (c)(i), (d)(i) and (ii) of paragraph 1 results in a fraction of days, the withdrawal period shall be rounded up to the nearest number of days."

Owners of treated animals have to be informed about withdrawal periods prescribed by the responsible veterinarian.

3.4. Record-keeping by owners and keepers of food-producing animals

Owners and keepers of food-producing animals have to keep detailed records (log book) on pharmacotherapeutic treatments of their animals (Art. 108). If the information to be recorded is already available on the copy of a veterinary prescription, it may also serve as the respective document. The items to be logged shall be available for inspection by the competent authority for at least 5 years and include:

(a) "a) date of the first administration of the medicinal product to the animals;
(b) name of the medicinal product;
(c) quantity of the medicinal product administered;
(d) name or company name and permanent address or registered place of business of the supplier;
(e) evidence of acquisition of the medicinal products they use;
(f) identification of the animal or group of animals treated;
(g) name and contact details of the prescribing veterinarian, if applicable;
(h) withdrawal period even if such period is zero;
(i) duration of treatment."

These records may serve (on the national level) as basis for the obligatory calculation of the antimicrobials used for the purpose of official surveillance of consumption.

4. Discussion

The European surveillance system project on collection of sales of veterinary antimicrobial consumptions (ESVAC) allowed the estimation of sales of veterinary antimicrobials in Member States of the European Union and European Economic Area. The project was started by EMA in 2009 and collected information on how much antimicrobial veterinary medicinal products were sold in animals across the European Union

(EU). This information is regarded essential to "identify possible risk factors that could lead to the development and spread of antimicrobial resistance in animals."

In its 12th annual report published in November 2022 about trends from 2010 to 2021, declines of sales (expressed in mg/PCU) of 37.8% for third and fourth generation cephalosporins, 79.5% for polymyxins, 14.2% for fluoroquinolones, 85% for other quinolones, all being Category A compounds, were reported for the 31 countries which have submitted the respective data (EMA, 2022b).

An interactive "European database of sales of veterinary antimicrobial agents" was launched in 2015. Its purpose is to provide public access to the data the ESVAC project collecting data on the sales of veterinary antimicrobials in Member States of the European Union and European Economic Area (EMA, 2022c).

In human medicine antimicrobial medicines use (AMU) monitoring is regulated for EU member states following Decision No 1082/2013/EU (Decision No 1082/2013/EU, 2013). Results are published on the European Centre for Disease Prevention and Control (ECDC) website (ECDC, website).

Starting from 2023 the ESVAC project is terminated. One more ESVAC report will be issued, including the 2022 sales data. The collection of Antimicrobial Sales and Use data (ASU) will be a formal task of the EMA and positioned under the responsibility of the CVMP, and the deadline for data submission for the first report is planned September 30th, 2024.

The objective of Regulation (EU) 2019/6 includes the "strengthening of the prudent use of antimicrobials by restricting the use of substances in animals which are of critical importance for preventing or treating life-threating infections in humans". Antimicrobials or groups of antimicrobials reserved for the treatment of certain infections in humans are designated by the Commission by means of implementing acts as formulated in Article 37 (5); criteria are postulated in Commission Delegated Regulation (EU) 2021/1760, and active substances fulfilling these criteria are designated in the annex of Commission Implementation Regulation (EU) 2022/1255 (Commission Impl. Regulation (EU) 2022/1255, Commission Impl. Regulation EU 2022/1255, 2022).

The use of an antimicrobial substance authorized for treatment of animals has to be clinically justified. For use of medicinal products outside the terms of marketing authorisation in companion animals or in food producing animals, additional rules are applicable. Treatment of food animals requires that for all medical substances contained in the product MRLs are set in accordance to Regulation (EU) 470/2009 (Reg. (EU) 470/2009, 2009) and published in Annex 1 of (EU) 37/2010 and that appropriate withdrawal times are observed or determined by the responsible veterinarian in case of use outside the marketing authorisation according to Article 155 of (EU) 2019/6. These rules provide opportunities to overcome existing therapeutic gaps in veterinary medicine while ensuring the requirements of public health (Fig. 1).

Further provisions are in place to diminish the risks connected to the emergence of resistance against antibiotics. These rules regulate the prescription, use, record keeping and (EMA) monitoring of the consumption of antimicrobial products. All Member States of the EU have to collect relevant and comparable data on antimicrobial medicinal products sold for and used in animals (Reg. (EU) 2019/6, Article 57). The

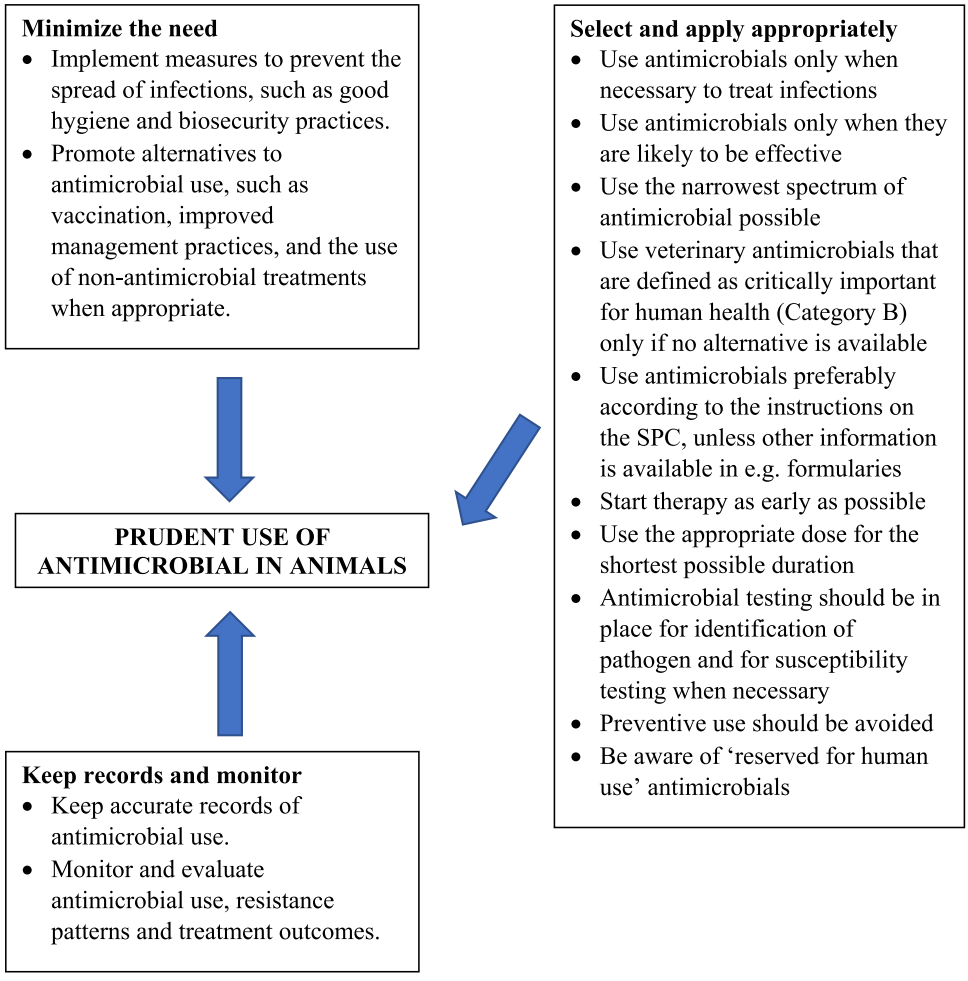

Fig. 1. Essential rules of prudent use of antibiotics in animals.
Legend: Category B, EMA Category B (Restrict), SPC., Specific Product Characteristics

data serve the evaluation of the use of antimicrobials, starting in 2023 for some sectors of food-producing animals but eventually extending to companion animals in 2029, at national level. The "collated data on the volume of sales and the use per animal species and per types of antimicrobial medicinal products used in animals" have to be send to the EMA for analysis and annual report. Recently EMA published the protocol for the collection of antimicrobial sales and use data (ASU) (EMA, 2022a). The responsible national authorities should report data for use in cattle, pigs, chickens, and turkeys, additionally to total antimicrobial VMP sales data. In some Member States the system for collecting use data in cattle, pigs and poultry is already in place, but it should be ready for reporting over 2023 in all MS's and involves veterinarians (Article 105), keepers and owners of food producing animals (Article 108), manufacturers and wholesale distributers (Article 58 (11); Article 96, Article 101) and Member States (Article 57).

EU 2019/6, 2019 also refers to the many aspects of marketing authorisations including the applications for limited markets, obligatory data to be submitted, its different procedures, post marketing authorisation measures, collection of data on antimicrobial medicinal products used in animals, environmental safety and pharmacovigilance systems and Union data bases (e.g., Union Pharmacovigilance (veterinary medicines) (Commission Impl. Regulation EU 2021/1281, 2021). This Regulation applies from January 28, 2022, and is going into effect gradually until 8 years after this date. At an "EMA Veterinary Medicines Infoday" held online in February 2023 different interested stakeholders presented their perspectives on the implementation progress of it. There was fundamental agreement with the new regulation on the part of the industry and the progress was valued (e.g., good joint collaboration between EMA, national competent authorities (NCAs), and industry). Notwithstanding a positive attitude, serious concerns and worries were articulated among them underestimated administrative burden and workload. "It will be still some time until we can say with confidence that we trust the databases and that we have well established procedures to fulfil our legal obligations" (EMA, 2023).

During the EMA Second Veterinary Big Data stakeholder forum in November 2022 the Federation of Veterinarians of Europe (FVE) addressed topics related to issues touched upon later on the EMA Info day mentioned (EMA, 2022d). Among these were shortages in lower class antibiotics and alternatives to antibiotics, incomplete SPC harmonisation and modernization, decrease in administrative burden for users, improvements in integration of the One Health approach and interdisciplinary One Health collaboration.

The third joint inter-agency report "Integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals" covering 29 countries the EU/EEA indicated for 2017 that the overall consumption of active substance was one third higher in food-producing animals than in humans, while the estimated biomass of food-producing animals was twice as high as the estimated biomass for humans" (expressed in tonnes active antimicrobial) (ECDC, EFSA, EMA, 2021). As a consequence, with AMU expressed in biomass-corrected consumption (mg/kg biomass) the overall mean use of antimicrobials in animals was lower for most of these countries. For 2017-2018 "the overall mean antimicrobial consumption was higher for humans than in food-producing animals."

In a global study significant associations between antimicrobial consumption and antimicrobial resistance (AMR) in food producing animals and between human antimicrobial consumption and AMR specifically in WHO critical and high priority pathogens were reported by Allel et al. (2023). "Animal antibiotic consumption was positively linked with animal AMR." The authors have conceded the complexity of the causes of AMR and gaps of knowledge. The authors stated that "antimicrobial consumption in animals was significantly associated with resistance in WHO critical priority human pathogens and antimicrobial consumption in humans was significantly associated animal AMR rates".

As an overall statement it can be said that a scientific body of knowledge supports the conclusion that the rules of prudent use are among the most valuable tools for minimising the occurrence of AMR. With the reduction of the use of antimicrobials in animals that has taken place in recent years Veterinary Medicine as a whole has moved in the right direction.

It was the intention of this article to accentuate and quote essential aspects and legal provisions regarding the on-site-use of VMPs by veterinary practitioners/animal owners - one of the most critical steps in achieving prudent use antimicrobial VMPs.

CRediT authorship contribution statement

Ivo Schmerold: Conceptualization, Writing – original draft, Writing – review & editing. **Inge van Geijlswijk:** Writing – original draft, Writing – review & editing. **Ronette Gehring:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

Data availability

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