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USE OF TETRACYCLINES AND SULFONAMIDES FOR THE TREATMENT OF INFECTIOUS DISEASES IN ANIMALS

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The use of antimicrobial medicines in human and veterinary medicine has led to the problem of the development of acquired antimicrobial resistance, which causes a global threat. Were described principles of tetracyclines and sulfonamides use, which are the most common among antimicrobial substances in veterinary medicinal products for the treatment of infectious diseases of food-producing and domestic animals.

The aim. *To substantiate the clinical relevance of antimicrobial veterinary medicinal products containing tetracyclines and sulfonamides+trimethoprim in veterinary medicine.*

Materials and methods. *Research materials: sales reports of antimicrobial veterinary medicinal products in Ukraine for 2015–2019, EU countries, and the USA. Methods used: written and electronic survey; bibliosemantic, analytical and generalization.*

Results and discussion. *As a result of the annual monitoring for 2015–2019 sales volumes in Ukraine, it was determined that tetracyclines (29.5–37.91 %) and sulfonamides + trimethoprim (12.1–18.7 %) were most often used in the composition of veterinary medicines. The same trend regarding the use of these classes of antimicrobials exists in many countries around the world. Factors determining the clinical relevance of these groups of substances are based on the criteria for their selection.*

The principle proposed by the EMA for the choice of antimicrobial veterinary medicinal products is based on the following criteria: categories of target animal species; treatment indications; the route of administration; the type of pharmaceutical formulation; the choice of a dosage regimen. Following this principle was substantiated the feasibility of tetracyclines and sulfonamides+trimethoprim use in veterinary medicine.

By pharmacokinetic and pharmacodynamic parameters evaluated the rationality of the choice of antimicrobial veterinary medicines.

Conclusions*. The study revealed clinical efficacy and safety of tetracyclines and sulfonamides+trimethoprim as Veterinary Critically Important Antimicrobial Agents of Category D "Prudence"*

Keywords: *tetracyclines, sulfonamides+trimethoprim, pharmacokinetic parameters, withdrawal period, maximum residue limits*

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1. Introduction

The use of antimicrobial medicinal products (AMPs) in the practice of human and veterinary medicine has led to a problem known as the development of acquired antimicrobial resistance (AMR), which poses a global threat. Although the use of AMPs in human and veterinary medicine is regulated by current legislation, the threat of the accelerated spread of the acquired AMR is great [1, 2]. Preventive and overcoming measures for the acquired AMR are urgent, both at the national [1] and at the international level [3, 4]. Ukraine has joined the measures substantiated in the Global Action Plan on combating the acquired AMR. The World Organization for Animal Health (OIE) worked out global Action Plan in collaboration with the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), according to which the One Health concept was introduced in 2015. The European Medicines Agency (EMA), mutually with the Committee for Veterinary Medicinal Products (CVMP), has submitted for discussion in the EU Member States a new strategy on antimicrobials for 2021–2025 [4]. Resolution of the Cabinet of Ministers of Ukraine of March 6, 2019, No. 116-r approved "National Action Plan Tackling Antimicrobial Resistance" (hereinafter referred to as the "Plan"). This "Plan" has identified the main assignments for the AMP rational use in human and animal healthcare [1]. The National Agency for Veterinary Medicinal Products and Feed Additives (hereinafter referred to as the Agency) adapted the OIE recommendations for data collection and implementation of a system for monitoring the circulation of antimicrobial veterinary medicinal products (AVMP) in Ukraine. As in most countries a qualitative and quantitative assessment conduct to interpret the patterns and trends in the use of AVMP, which is grounded on sales volumes based on monitoring results [5]. The Agency submits an annual re-

port to the OIE in the appropriate format. The Agency collected and processed data on the circulation of AVMP in Ukraine during 2015–2019 by written and electronic reporting. The data were provided voluntarily by AVMP domestic and foreign marketing authorization holders (MAHs) and distributors for the calendar year (from 01.01 to 31.12), previous to the current. Sales data are available, more or less complete and unbiased, and still the most optimal for comparison between the countries [5–8]. The analysis expressed by the antimicrobial class of data reported by MAHs and distributors revealed some trends. Products containing derivatives of tetracyclines (29.5–37.9 %) and sulfonamides (12.1–18.7 %) dominated among all classes of AVMP which were sold in Ukraine during all 5 years of the study. They are presented in pharmaceutical forms of systemic (solutions for injection, oral administration forms) and local action (ointments, liniments, sprays, eye, and ear drops). Conferring the MAHs and distributors data, in the sales amounts in Ukraine most common oral dosage forms were among tetracyclines and sulfonamides: chlortetracycline – 46.5 %, doxycycline – 41.7 %, oxytetracycline – 5.9 %; sulfanilamides + trimethoprim – 95.2 %. The proportion of injections of oxytetracycline was 3.8 %, and sulfonamides+trimethoprim– 2.3 %. Local action dosage forms of these AVMP were not taken into account in the study, as their share in sales was ± 1 %.

The annual sales data analysis for these groups of pharmacologically active substances can state a similar trend for the AVMP market in Europe and North and South America [5, 9–12]. However, for a more accurate comparison, it is necessary to take into account differences in the animal demographic characteristics, the number of livestock, appropriate keeping conditions, frequency of infectious diseases, and patterns of AVMP use [5, 7], and apply the appropriate indicators to quantify consumption [13].

The aim of the research is to substantiate the clinical significance of AVMP containing tetracyclines and sulfonamides for veterinary medicine.

2. Materials and methods

Methods used: a written and electronic survey of MAHs and distributors in a standardized form; bibliosemantic, analytical, and generalization.

For the analysis of pharmacokinetic parameters, dosage regimens, withdrawal periods of the residues were used the short characteristics of the products registered in Ukraine, and search systems: PubMed, ScienceDirect. EMA / ESVAC, FDA, OIE annual reports on the circulation of AVMP in Ukraine and the EU member states, the USA, legislative documents, and guidelines allowed to summaries the trends of AVMP use by influence factors.

3. Research results

Important factors substantiating the use of AVMP are their efficiency, safety, and economic standpoint. The choice of AVMP class depends on the isolation and dissemination of bacterial strains, which have become resistant to certain antimicrobial substances (resistant bacteria). To prevent inefficient use of AVMP, it is necessary to take into account the resistance of isolated bacterial strains to these veterinary products. When choosing a class of antimicrobials, consider: (1) the importance of the substance in veterinary medicine (for example, in the presence of alternatives), (2) the zoonotic significance of infectious diseases, and (3) the risk of transmission of resistant bacteria to humans [14, 15]. The WHO Advisory Group on Integrated Antimicrobial Resistance Surveillance (AGISAR) recommends the limited use of antimicrobials, which are the only or few substances that are effective against serious diseases or effective against zoonotic agents. AGISAR distinguishes three groups from all antimicrobials: important, very important, and critical [16, 17]. The FAO / OIE / WHO Working Group on Non-Human Antimicrobials has proposed a List of Critical Antimicrobials for Veterinary Medicine [15]. A special Antimicrobial Advise *ad hog* Expert Group (AMEG) has scientifically substantiated and proposed a new additional classification that takes into account the risk of their clinical effectiveness [15, 18]. According to this classification, among the important and critical antimicrobials recommended for use in veterinary medicine, there are four categories: A – Avoid; B – Restrict; C – Caution; D – Prudence. Additional classification of antimicrobial substances is included in the "Procedure for the use of antimicrobials in veterinary medicine" developed in Ukraine, which is being approved by the competent authorities.

Following the OIE categorization and AMEG, tetracyclines and sulfonamides are classified as Veterinary Critically Important Antimicrobial Agents (VCIA) of category D, as they are necessary for the treatment of many species of terrestrial animals and aquaculture [15, 18–20]. Tetracyclines and sulfonamides considered to be most widely used to treat several respiratory infections, digestive, and urogenital systems, dermal, and joints infections of animals [19–21]. Prerequisites for the widespread use of tetracyclines and sulfonamides for the treatment of food-producing animals and pets in domestic and foreign veterinary practice are also their pharmacological properties – their broad-spectrum of activity, i.e. active against gram-negative (*Neisseria spp., Moraxella spp., Yersinia spp., Brucella spp., Vibrio spp., Haemophilus spp., Actinobacillus spp., Bordetella bronchiseptica, Pasteurella spp., Fusobacterium spp.*), and gram-positive (*Staphylococcus spp., Streptococcus spp., Diplococcus spp., Listeria spp., Bacillus spp., Corynebacterium spp., Erysipelothrix spp., Actinomyces spp.*) microorganisms. They have been active against *Mycoplasma* (in particular *Mycoplasma hyopneumoniae, M. gallisepticum* and other), some protozoa; have low toxicity and good permeability in most tissues and body fluids by systemic administration.

To isolate the causative agent of infectious disease and study its sensitivity to AVMP requires from one to several days, which is not always convenient. Treatment should be started based on a preliminary diagnosis, considering the epizootic situation on the farm. At this stage of the disease are used AVMP category D or complex formulations. After receiving the results of the susceptibility to the pathogen, justify the need to continue the use of AVMP or its replacement.

Following EMA recommendations, the data needed for the AVMP choice will be collected at the level:

animal species – indication – route of administration – pharmaceutical form [14]. This principle causes minimal disruption of the AVMP market.

The modern approach of the systemic action AVMP dose and route of administration adjustment is based on the assessment of the pharmacokinetic parameters and pharmacodynamic efficacy ratio PK/PD [14, 22]. With other pharmacodynamics parameters, the *in vitro* susceptibility data, Minimal Inhibitory Concentration (MIC) should be compared with the concentration of the active substance in the relevant biophase (target tissue). For all systemic action AVMP, if available from pharmacokinetic studies, the PK/PD relationship should be determined. Because only the unbound antibiotic fraction *f* has antibacterial activity, its concentration available in biophase or serum/blood plasma is taken into account. Among the pharmacokinetic parameters are estimated, the relationship among the fraction of the area under the pharmacokinetic curve and MIC (*f*AUC/MIC), the highest concentration and MIC (fC_{max}/MIC), and time during which the concentration exceeds the threshold (*f*T >MIC). These pharmacokinetic parameters are mutual and could be compared with the AVMP MIC for a specific pathogen. If there are no subscripts indicating a time interval, it is assumed that the calculations of AUC and T>MIC grounded on a 24-hour interval at pharmacokinetic steady-state conditions [14]. The universal parameter for optimizing the dosage regimen for time-depended antibiotic could be AUC/MIC index [14].

In addition to the pharmacokinetic profile of AVMP are considered pharmacodynamic parameters, namely: the mechanism of action of the pharmacologically active substance (bacteriostatic or bactericidal) against target bacteria and antibiotic classes, time or concentration dependence of action. An important characteristic is the AVMP plasma proteins binding degree, in particular tetracyclines (oxytetracycline – 30 %; tetracycline – 60 %, doxycycline – 90 %) [19]. Achieving the target of bacteria growth inhibition up to 90 % is considered acceptable to justify the dose of AVMP.

The pharmacokinetic profile of the AVMP depends on their route of administration, species categories, and animal age, and are characterized by the parameters listed in Tab. 1 [23]. The pharmacokinetic parameters depend also on the activity duration in certain types of pharmaceutical forms: short-term or long-term (prolonged) action [24]. Tab. 1 presents the average values of the main pharmacokinetic parameters without specifying the types of pharmaceutical forms. These parameters characterize the distribution and elimination of tetracycline derivatives that are well-absorbed, especially fat-soluble (doxycycline) substances, which are characterized by a significant volume of distribution in tissues and organs and excreted in urine (50–80 %) and bile (10–20 %) as by oral and by injection.

Table 1

Pharmacokinetic parameters of antimicrobials in different animal species.

Antimicrobial substance	Animal species	Half-life of elimination, $t_{1/2}$, h	Volume of distribution, Vd, ml/kg	Clearance, Cl, ml/kg/h
Oxytetracycline	Calves (up to 3 months of age)	10–13	1 500–2 400	3.45
	Cattle	7–10	800–1 000	3.33
	Horses	8–10	1 100	2.89
	Dogs	6	3 000	4.23
Doxycycline	Horses	9	–	–
	Dogs	7–10	930	1.7
	Cats	5	340	1.0

The half-life of elimination for tetracyclines in AVMP depends on the age of the animals, the stage of disease and indicates the sufficiency of a single injection during the day to achieve an effective inhibitory concentration. As mentioned above, tetracyclines and sulfonamides are used mainly in oral pharmaceutical forms (over 95 %) in Ukraine due to convenient administration in animals, as well as the degree of bioavailability (BA) of pharmacologically active substances. In particular, the BA of chlortetracycline when administered orally to calves is 37 %, while oxytetracycline – 5 %, which is usually used in the form of a long-acting injection solution [14, 23]. The presence of milk or its substitutes in feed, polyvalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}, Al^{3+}), kaolin, and pectin, iron preparations significantly reduces the BA of tetracyclines. Sulfonamides (other than those active in the intestine) are well absorbed when administered orally to dogs, cats, and poultry, as determined by their solubility. In pigs and ruminants, the absorption time of sulfonamides is longer and significantly slowed down in milk-fed calves [23]. Sulfonamides, like tetracyclines, are protein-bound in the range of (15–90 %), depending on the species category, which affects the duration of elimination half-life [20].

The selection of AVMP dosing regimen depends on animal species and their age [7, 25, 26]. Notably, to calculate the steady-state concentration of sulfonamides equal to 100 μg/ml, it is necessary to take into account the degree of protein binding, the volume of distribution and the elimination half-life, as it differs significantly from the animal species. Thus, the elimination half-life of sulfadiazine in cattle is 10.1 hours, and in pigs – 2.9 hours. Usually, the difference in the rate of elimination for different animal species is due to the recommended doses and dosage regimen. However, the difference in dosing regimen come not only from differences in antimicrobial metabolism in different species and differences in body mass but also to accepted models of

keeping animals on farms (intensive and extensive conditions with different population densities) and schemes for the AVMP usage. For example, sheep and goats are kept in free walk farming systems, which provide them with good conditions for growth in good health. In contrast, pigs and poultry are kept in intensive growing conditions with short life cycles, high population density, which causes an insufficient level of immune response and leads to more frequent development of infectious diseases that require the use of AVMP. Doses in Table 2 are given following the Veterinary Manual [19, 20] and the summary of product characteristics (SPC) of AVMP authorized in Ukraine.

The recommended doses of the Veterinary Manual and SPC are slightly different, which can be explained by the animal keeping models, demographic characteristics of the animals, and the accepted dosing regimens.

Table 2

Dosage of antimicrobial substances

Antimicrobial substance	Animal species	Dose, route of administration, dosing interval, duration of administration	
		By the Veterinary Manual	By the SPC
Doxycycline	Pigs, poultry		10–20mg/kg, or., 3–5 days
	Dogs	5–10 mg/kg/day, or.	
		5 mg/kg/day, i/v.	
Oxytetracycline	Dogs, cats	7 mg/kg i/m or i/v., 2 × day	
		20 mg/kg or., 3 × day	10 mg/kg or., 3 × day
	Cattle, sheep, pigs	5–10 mg/kg/day i/m or i/v	20 mg/kg/day i/m or i/v
	Calves, foals, lambs, piglets	10–20 mg/kg i/m, 2–3 × day	
	Horses	5 mg/kg i/v, 1 or 2 × day	
	Pigs		20–50 mg/kg/day i/m
	Poultry		40–70 mg/kg/day or.
Tetracycline	Dogs, cats	7 mg/kg i/m or i/v, 2 × day	
		20 mg/kg or., 3 × day	
Chlortetracycline	Calves		20 mg/kg or., 3–5 days
Succinyl sulfthiazole	All species	160 mg/kg or., 2 x day (initial dose – ½ from subsequent doses)	
Sulfadiazine + trimethoprim	All species	15–60 mg/kg/day, or., i/v, i/m	(25+5) mg/kg or., 3–5 days
Sulfadimethoxine	All species	55 mg/kg/day, or. (initial dose – ½ from subsequent doses)	18,68-37,36 mg/kg or., 3–5 days
Sulfadimethoxine + trimethoprim	All species		(16,68–37,36+4–8) mg/kg, or., 3–5 days; (20+4) mg/kg, i/m
Sulfamethazine	Cattle	220 mg/kg/day, or., i/v (initial dose – ½ from subsequent doses)	
	Cattle, pigs, sheep, dogs, cats		200 mg/kg or., 3–5 days
Sulfamethoxypyridazine	Cattle	55 mg/kg/day or.	
	Pigs	110 mg/kg/day or. (initial dose – ½ from subsequent doses)	
Sulfapyridine	Cattle	132 mg/kg or., 2 x day (initial dose – ½ from subsequent doses)	
Sulfathiazole	Horses	66 mg/kg or., 3 x day	
	Cattle, sheep, pigs	66 mg/kg or., every 4 h.	

Certainly, the lower the dose of AVMP and the shorter duration of administration, the less they are used in practice [13]. It is very important to have data on the susceptibility of the bacteria to the administered doses of AVMP, which are determined experimentally during clinical trials and post-registration studies.

These studies contribute to the optimal dose choise and intervals of their administration to ensure an effective bactericidal or bacteriostatic concentration of pharmacologically active substances in the body [14].

The problem of reducing the use of AVMP is particularly acute under conditions of intensive animal hus-

bandry due to increased biosecurity and improved hygiene of animals, which also involves genetic selection and other aspects of farm management. As for the level of AVMP usage in mass value, it will be higher for AVMP, which are used in higher doses, as well as for animals with high body mass, needed to be treated in large populations.

An important parameter that characterizes the safety of the AVMP for food-producing animals is the withdrawal period (WP), i.e. the time during which the tissues and organs set the maximum acceptable residue limits of the pharmacologically active substances (MRLs) [27]. This parameter is directly related to the dose of systemically administered AVMP as well as the type of pharmaceutical form because the latter has a significant effect on the rate and completeness of absorption.

The withdrawal period indicates the longest time, which is counted after the last administration of AVMP for animals to achieve the maximum acceptable residue levels (MRLs) of pharmacologically active substances. Determination of WP for AVMP residues is necessary for the safe use of products of animal origin after treatment of food-producing animals. This parameter is indicated in the SPC and the package leaflet. The withdrawal period depends on several factors, the most important of which are the animal species, their age, body weight, husbandry and feeding conditions, and health status. However, taking into account these factors, the determination of WP is costly, so they are limited by the ratio (ADI/MRLs): acceptable daily intake of food (ADI) to the maximum residue limits (MRLs) of pharmacologically active substances in animal products. The maximum residue limits of pharmacologically active substances are defined in the EU by Regulation (EU) No. 37/2010 of 22 December 2009, and in Ukraine by the List of Indicators, which is harmonized under this Regulation and approved by Order of the Ministry of Health of Ukraine No. 2646 of 23.12.2019 [28]. Food products of animal origin and/or ingredients of animal origin may not be in turnover if they contain residues of AVMP above the maximum residue limits listed in Table 3. The WP data in Table 3 are presented following the Veterinary Manual (VM) [9, 10] and SPC, and the maximum residue limits (MRLs) – according to the Order of the Ministry of Health of Ukraine No. 2646 dated 23.12.2019 [28].

Table 3

The withdrawal period and maximum residue limits of antimicrobials in meat and milk

Antimicrobial, route of administration of AVMP	Animal species	Withdrawal period, days		Target tissues [28]	Maximum residue limits, mcg/kg [28]
		VM	SPC		
1	2	3	4	5	6
Doxycycline, oral	All food-producing animals Pigs, poultry		 7	Meat Fat Liver Kidneys	100 300 300 600
Oxytetracycline, oral	All food-producing animals		6–10	Meat Fat Kidneys Milk Eggs	100 300 600 100 200
Oxytetracycline, i/m	Cows	15–22	30		
	Pigs	22	23		
	Poultry	5			
	Goat, sheep		24		
Oxytetracycline * (long-acting)	Cows	28			
Chlortetracycline	All food-producing animals Calves		 12	Meat Liver Kidneys Milk Eggs	100 300 600 100 200
	Cows, meat, milk	10	7		
	Pigs	1–7			
Sulfamethazine	Cattle	10			
	Pigs	14			
Sulfamethazine, i/m	Pigs, cattle		28		
	Cows, milk		4		
Sulfamethazine, oral	Pigs, cattle		5		
	Cows, milk	4			
Sulfamethazine (long-acting boluses)	Cattle	28			
Sulfadimethoxidine, or.	Cattle	7	12		
	Cows, milk	60 hours			
Sulphonamides (all substances belonging to the group of sulphonamides)	All food-producing animals			Meat Fat Liver Kidneys	100 100 100 100

Continuation of Table 3

1	2	3	4	5	6
	Cows, sheep, goat			Milk	100
Triplet solution of sulphonamides (8 % sodium sulfamethazine, 8 % sodium sulfapyridine, 8 % sodium sulfathiazole)	Cattle	10			
	Cows, milk	4			
Trimethoprim	Horses			Meat Fat Liver Kidneys	100 100 100 100
	All food-producing animals			Meat Fat Liver Kidneys Milk	50 50 50 50 50
Trimethoprim / sulfadiazine	All animal species	3	12		
	Cows, milk	7			
Trimethoprim / sulfadimethoxine, oral	All animal species		12		
Trimethoprim / sulfadimethoxine, i/m	All animal species, milk		7 4		
Trimethoprim / sulfadoxine, oral i/m	All animal species	5 28			

*Note: *– long-acting dosage forms not recommended for use in cows whose milk is intended for human consumption [28]; data approved by the Order of the Ministry of Health of Ukraine No. 2646 dated 23.12.2019*

Listed in Tab. 3 WP for oxytetracycline long-acting pharmaceutical form from cow's milk does not meet the commonly accepted time criteria for milk (7 days) [27]. Therefore, it is recommended to use long-acting AVMP for cows during the drying-off period because long-term utilization of milk causes economic losses to farms.

4. Discussion of research results

It is important to note that for the determining of the WP should be considered the elimination of the residues from the site of the injection where the AVMP was administered subcutaneously (s/c) or intramuscular (i/m). Studies provided by Achenbach T. E. who applied the physiological pharmacokinetic model showed, that the subcutaneous administration for cattle 20 % solution of long-acting oxytetracycline at a dose of 20 mg/kg b.m. and the maximum injection into one injection site of 10 ml the WP regarding residues of this substance reaches 28 days, and in muscles can last up to 35 days due to the possibility of protein-binding, an affinity for muscle fibers, blood flow to tissues because of physical activity [29].

Excipients may induce the local irritant effect of AVMP and this should be considered for AVMP-generics when the volume of solution is injected into one injection site should be increased [14]. The choice of route of administration is usually determined by the veterinarian, as it is important to consider the possibility of irritation or swelling at the injection site.

Achenbach T. E. confirmed the same bioavailability of oxytetracycline by s/c and i/m injection administration, which allows alternatively applying a solution of oxytetracycline by s/c injection to reduce the concentration at the injection site [29]. In practice, during the slaughter of animals, the tissues that were injected are removed to prevent possible entering the residues of pharmacologically active substances from products intended for human consumption.

Substantiation of the rational AVMP use, grounded on the requirements of efficiency and safety for animals, veterinary professionals, and humans consuming the products of animal origin, is the first step to assess their impact on the possibility of developing the acquired antimicrobial resistance. For prudent use of AVMP and application of the appropriate regimen of treatment is necessary to consider the data obtained in pharmacokinetic research, which also are helpful to avoid contamination of consumers with the residues of the pharmacologically active substances across the food chain.

The threat of the acquiring of resistant bacterial strains and the environmental safety of AVMP use is another problem.

Study limitations. Data on the amounts of AVMP was based on a voluntary survey reported by marketing authorization holders and distributors on sales volumes. These data are not differentiated for animal species. The study was limited to the use of AVMP by animal species.

Prospects for further research. Necessary to consider global trends in lowering the amounts of AVMP used for the treatment of infectious diseases when substantiating the rational use of tetracyclines and sulfonamides + trimethoprim. All stakeholders (from production to the consumption of AVMP) should be involved in providing the research. Veterinarians have the most important role in this process as key professionals who are making decisions in the choice and prescription of AVMP. The plans for the future are to obtain data on the use of AVMP of these antimicrobial classes by animal species.

5. Conclusions

Data from the literature, scientific reports, and the results of our research confirm the possibility of using AVMP, which contains tetracyclines and sulfonamides + + trimethoprim, well known in clinical veterinary practice. In the Ukrainian market, these AVMP prevail (95 %) in systemic pharmaceutical forms for oral administration. The possibility of their widespread use in veterinary medicine is confirmed by pharmacokinetic and pharmacodynamic characteristics, tolerance, and low toxicity for many species of animals, as well as inclusion in the list of Veterinary Critically Important Antimicrobial Agents (VCIA) Category D.

The nonappearance of residues of antimicrobial pharmacologically active substances in foodstuffs intended for human consumption is regulated by the maximum residue limits and the withdrawal period, which are also determined as a result of pharmacokinetic studies. The safety of food of animal origin directly depends on the rational use of AVMP.

Conflicts of interests

The authors declare that they have no conflicts of interest.

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