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

How to cite:
Kosenko, Y., Bilous, S., Ostapiv, N., Zaruma, L. (2021). Use of tetracyclines and sulfonamides for the treatment of infectious diseases in animals. ScienceRise: Biological Science, 2 (27), 1017. doi: http://doi.org/10.15587/2519-8025.2021.235057

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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: chlorotetracycline – 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 %.

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 bacte-rial 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 Critically Important Antimicrobials for Veterinary Medicine [15]. A special Antimicrobial Advisory 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, dental, 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 and 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 bronchi- septica, Pasteurella spp., Fusobacterium spp.), and gram-positive (Staphylococcus spp., Streptococcus spp., Diploroccus spp., Listeria spp., Bacillus spp., Coryne- bacterium 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:

Scientific Journal «ScienceRise: Biological Science» №2(27)2021

Biological research
characterized by the parameters f, C_{\text{max}}, \text{AUC} \text{MIC}, \text{AVMP dose} \text{MIC}

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 (fAUC/MIC), the highest concentration and MIC (C_{\text{max}}/MIC), and time during which the concentration exceeds the threshold (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-dependent 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 oral and by injection.

| 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 |
|                        | 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

| Antimicrobial substance | Animal species                  | Dose, route of administration, dosing interval, duration of administration |
|-------------------------|---------------------------------|-------------------------------------------------------------|
|                         |                                 | By the Veterinary Manual | By the SPC          |
| Doxycycline             | Pigs, poultry                   | 10–20 mg/kg/day, or.                          | 20 mg/kg/day 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                      | 10 mg/kg or., 3 × day   |
|                         | Cattle, sheep, pigs             | 20 mg/kg or., 3 × day                             | 20 mg/kg/day i/m or i/v |
|                         | Calves, foals, lambs, piglets   | 10–20 mg/kg i/m, 2–3 × day                        | 10 mg/kg or., 3 × day   |
|                         | Horses                          | 5 mg/kg i/v, 1 or 2 × day                         | 20–30 mg/kg/day i/m     |
|                         | Pigs                            | 5 mg/kg i/v, 1 or 2 × day                         | 20–30 mg/kg/day i/m     |
|                         | Poultry                         | 40–70 mg/kg/day or.                              | 20–50 mg/kg/day i/m     |
| Tetracycline            | Dogs, cats                      | 7 mg/kg i/m or i/v., 2 × day                      | 20 mg/kg or., 3 × day   |
|                         |                                 | 20 mg/kg or., 3 × day                             | 20 mg/kg or., 3–5 days  |
| Chlortetracycline       | Calves                          | 160 mg/kg or., 2 × day (initial dose – ½ from subsequent doses) | (25+5) mg/kg or., 3–5 days |
| Succinyl sulphathiazole | All species                     | 15–60 mg/kg/day, or., i/v, i/m                    | 18,68–37,36 mg/kg or., 3–5 days |
| Sulfadimethoxine        | All species                     | 55 mg/kg/day, or. (initial dose – ½ from subsequent doses) | (16,68–37,36+4–8) mg/kg, or., 3–5 days; (20+4) mg/kg, i/m |
| 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) | 200 mg/kg or., 3–5 days |
|                         | Cattle, pigs, sheep, dogs, cats | 220 mg/kg/day, or., i/v (initial dose – ½ from subsequent doses) | 200 mg/kg or., 3–5 days |
| Sulfmethoxypyridazine   | Cattle                          | 55 mg/kg/day or.                                  | 200 mg/kg or., 3–5 days |
|                         | Pigs                            | 110 mg/kg/day or. (initial dose – ½ from subsequent doses) | 110 mg/kg/day or. (initial dose – ½ from subsequent doses) |
| Sulfapyridine           | Cattle                          | 132 mg/kg/day, or. (initial dose – ½ from subsequent doses) | 132 mg/kg/day, or. (initial dose – ½ from subsequent doses) |
| Sulphathiazole          | Horses                          | 66 mg/kg or., 3 × day                             | 66 mg/kg or., every 4 h. |
|                         | Cattle, sheep, pigs             | 66 mg/kg or., every 4 h.                          | 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 choice 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-
bandy 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].

| 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 | 7 | Meat | 100 |
|                | Pigs, poultry | | Fat | 300 |
|                | | | Liver | 300 |
|                | | | Kidneys | 600 |
| Oxytetracycline, oral | All food-producing animals | 6–10 | Meat | 100 |
|                | | | Fat | 300 |
|                | | | Kidneys | 600 |
|                | | | Milk | 100 |
|                | | | Eggs | 200 |
| Oxytetracycline, i/m | Cows | 15–22 | 30 | Meat | 100 |
|                | Pigs | 22 | 23 | Fat | 300 |
|                | Poultry | 5 | | Kidneys | 600 |
|                | Goat, sheep | | | Milk | 100 |
|                | | | | Eggs | 200 |
| Oxytetracycline * (long-acting) | Cows | 28 | | | |
| Chlortetracycline | All food-producing animals | | Calves | 12 | |
|                | Cows, meat, milk | 10 | 7 | Meat | 100 |
|                | | | Pigs | 1–7 | Fat | 300 |
|                | | | | | Liver | 300 |
|                | | | | | Kidneys | 600 |
|                | | | | | Milk | 100 |
|                | | | | | Eggs | 200 |
| Sulfamethazine | Cattle | 10 | | | |
| Sulfamethazine, i/m | Pigs | 14 | | | |
| Sulfamethazine, oral | Pigs, cattle | 28 | | | |
|                | 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 | | | |
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.

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**Table 3**

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

Financial support
The study was performed without financial support.

Acknowledgment
The authors would like to acknowledge foreign and domestic marketing authorization holders and distributors for their participation in the program of antibiotics monitoring in Ukraine and providing the data for the period of 2015–2019.

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Received date 27.04.2021
Accepted date 25.05.2021
Published date 30.06.2021

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