**History of antibiotic development as medicines**

**In 1928**, the first antibiotic (penicillin) was discovered by Alexander Fleming. However, it took over a decade before penicillin was introduced as a treatment for bacterial infections. In **1930s**, a sulfonamide (Prontosil) was developed by the German biochemist Gerhard Domagk [[3]](https://www.reactgroup.org/toolbox/understand/antibiotics/development-of-antibiotics-as-medicines/#zp-ID-11291-280251-92UT5NQP). **1945**, Florey and Chain was introduced Penicillin on a large scale as a treatment for bacterial infections through efficiently purify the antibiotic and scale-up production. The introduction of penicillin marked the beginning of the so-called “golden era” of antibiotics. In **1940 – 1962**, most of the antibiotic classes (β-lactams, tetracyclines , aminoglycosides, and sulfonamides) were discovered and introduced to the market. Each class contains numerous antibiotics that have been discovered or modified of previous types. Today, there are very few novel antibiotics under development. At the same time antibiotic resistant bacteria are becoming more common, making available antibiotics ineffective.

**Antibiotics and their uses**

The term antibiotic comes from the phrase antibiosis means against life. Antibiotics are compounds that are produced naturally by one microorganism or produced synthetically in the laboratory. They are fight bacterial infections in people and animals either by killing the microorganism (bactericidal) or keeping them from proliferation themselves (bacteriostatic). They could be injected intravenously, intramuscularly, subcutaneously or administered orally in feed and water [[13](https://www.tandfonline.com/doi/full/10.1080/10942912.2016.1212874),[14](https://www.tandfonline.com/doi/full/10.1080/10942912.2016.1212874)].  Wide spectrum of antibiotics with different mechanisms of action is being using in animals as therapeutic agents to treat diseases. Use of antibiotic as therapeutic agents involves exposure of animal (either individually or in small groups) to high dose of antibiotic for relatively shorter periods. In addition, antibiotics are being using in animal as prophylactic agents when symptoms are not observed but infections are suspected. Use of antibiotic as prophylactic agents involves exposure of animal to moderate dose of antibiotic for longer time durations. Moreover, use of antibiotic as growth promoter in animal helps the consumers to have high quality meat and egg at reasonable price. Use of antibiotic as growth promoter involves exposure of animal to a low dose of antimicrobial for a very long duration or throughout the entire lifespan of the animals (Donoghue, 2003). Antibiotic growth promoters are inhibited the gut bacteria leaving more nutrients for animal to be absorbed for greater growth. Veterinary medicinal products should be administrated to animal appropriately in terms of authorised route of administration, dose of therapy, duration of treatment, and withdrawal periods required **for animal and its products**. Veterinary medicines along with their derivatives, mode of actions, indications, and sources are presented in Table 1.

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| **Antibiotic** | **Description** |
| β-lactams | **Derivatives:** Amoxicillin, penicillin, cephalosporin, ampicillin, monobactam, carbapenem  **Mechanism of action:** Binding to cytoplasmatic membrane enzymes. This inhibits a step in peptidoglican synthesis that is crucial for cell wall formation.  **Indications:** Omphalitis; Clostridial infections (necrotic enteritis, ulcerative enteritis, gangrenous dermatitis), Staphilococcosis, Pasteurellosis, Ornithobacterium rhinotracheale, intestinal spirochetosis, Erysipelas  **Recommended withdrawal time:** 6 days |
| Macrolide | **Derivatives:** Tylosin and Tilmicosin  **Mechanism of action:** Binding to the 50S subunit of the bacterial ribosome and inhibiting translocation of peptidyl-tRNA from the A site to the P site.  **Indications:** Mycoplasmosis Necrotic Enteritis Ornithobacterium rhinotracheale  **Recommended withdrawal time:** Tylosin: 8 days and Tilmicosin : 10 days |
| Aminoglycosides | **Derivatives:** Neomycin, Streptomycin, Spectinomycin, Gentamicin  **Mechanism of action:** Binding to the 30S subunit of the bacterial ribosome and inhibiting translocation of fMet-tRNA.  **Indications:** Enterobacter, Salmonella, Shigella and Pseudomonas aerugino  **Recommended withdrawal time:** 3 to 14 days |
| Fluoroquinolones | **Derivatives:** Enrofloxacin, Danofloxacin, Flumequine, Norfloxacin, Difloxacin  **Mechanism of action:** Inhibiting DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase.  **Indications:** Salmonellosis, Colibacillosis , Fowl cholera and Pseudomonas aeruginosa (enrofloxacin)  **Recommended withdrawal time:** 5 to 10 days |
| Tetracyclines  Picture of Tetracycline 3D model | **Derivatives:** Chlortetracycline Oxytetracycline Doxycycline  **Mechanism of action:** Binding to the 30 S subunit of the bacterial ribosome and inhibiting translocation of aminoacyl transfer-RNA.  **Indications:** Mycoplasma, Chlamydia, Pasteurella, Ornithobacterium rhinotracheale, Clostridium spp., Spirochetes and some protozoa.  **Recommended withdrawal time:** 5 days |

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| **Antibiotic** | **Description** |
| Sulfonamides | **Derivatives:** Sulfacetamide, sulfamethoxypyridiazine, sulfamethoxydiazine, sulfamethoxazole, sulfadimidine, suflamethoxine, sulfadiazine, sulfafurazole.  **Mechanism of action** Inhibiting utilization of resemble p-aminobenzoic acid, and hence dihydrofolate synthesis.  **Indications:** Gram-positive and gram-negative organisms as: Staphylococcus spp., Streptococcus spp., Pasteurella, Salmonella and E.coli.  **Recommended withdrawal time:** 5 days |

**Veterinary medicines and the safety of food derived from animals**

Veterinary medicines are active substances that are administrated to animals to protect their health. After veterinary medicinal products being administrated to an animal, most of the medications are excreted via urine and a lesser extent in feces. However, after excretion, portion of the medications may continue in animal tissues and its products for a certain period of time as residues. The use of veterinary medicines is controlled by European Law and required observance of the withdrawal period. The withdrawal period is a period of time after the last dose of the veterinary medicine has been administrated and before allowing the animal tissues or its produce for consumption by human. Withdrawal period reflects the period required for an animal to metabolise an administered antibiotic and the period required for the antibiotic concentration level in the tissues equal or lower than the maximum residue limit /safe. This practice provides an assurance that food from animals is safe for human consumption with regards residues of veterinary medicines. Once the withdrawal period has elapsed, the animal tissues or its products are safe for human consumption. Withdrawal periods for veterinary medicines are not the same for all antibiotics. In addition, withdrawal periods for veterinary medicines are specific for each farm species and food from animal (5). Moreover, withdrawal periods may be extended when combinations of antibiotics are used or when antibiotics are used in an extra-label manner. Each antibiotic that is administrated to animals have a withdrawal period. When an animal is administrated an antibiotic, the antibiotic fight bacteria and the body break done the antibiotic. This process takes different period for different antibiotics depending on chemical and physical properties of medications and route of administration. In addition, it takes different times in different animals. Some antibiotics have different break down times for different tissues. The withdrawal period can be found on the product leaflet (6). Veterinary medicinal products and their withdrawal period are presented in Table 2.

To determine the withdrawal period, the maximum residue limits are established for all medicine by the independent European Regulator for Veterinary Medicines (2, 3). European Medicines Agency and its Committee for Veterinary Medicinal Products are responsible for assessing the safety of residues from veterinary medicines available in the European Union.

The maximum residue limits are described as such that consumers can ingest large amounts of food from animal every day without exceeding the acceptable daily intake. The acceptable daily intake is the amount of the residue that is considered safe for an individual to eat every day for their lifetime taking into consideration a number of safety factors including the amounts of each food eaten per day and how the substance is metabolised and distributed in the animal tissues. A maximum residue limits are then set for each edible tissue and product to ensure the acceptable daily intake is not exceeded.

The maximum residue limit is the maximum concentration of an antibiotic residue accepted by the European Union in animal tissues and its product obtained from an animal that has received a veterinary medicine (2). The unit used for this maximum acceptable concentration is milligrams per liter of liquids and milligrams per kilogram for solid products [[12](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760505/#ref12)]. Meat and other edible products from animal, which contain antibiotic residues beyond the maximum residue limit, may cause serious health problems of the consumers [[13](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760505/#ref13)]. Good quality meat and other products from animal are required for maintaining proper public health [[14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760505/#ref14)]. Presence of antibiotic residues in food from animal and subsequent consumption can cause potential health impacts, such as cancer and hypersensitivity reaction along with development of bacterial resistance [[15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6760505/#ref15)]. The consequences of bacterial resistance are even more threatening where antibiotics become ineffective clinically. Maintaining proper withdrawal time, established for meat, and other food from animal can act as a protection to resist from hazardous impacts of antibiotic residues.

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| **Antibiotic** | **Description** |
| β-lactams | **Derivatives:** Amoxicillin, penicillin, cephalosporin, ampicillin, monobactam, carbapenem  **Recommended withdrawal time:** 6 days  **maximum residue limits:** |
| Macrolide | **Derivatives:** Tylosin and Tilmicosin  **Recommended withdrawal time:** Tylosin: 8 days and Tilmicosin : 10 days  **maximum residue limits:** |
| Aminoglycosides | **Derivatives:** Neomycin, Streptomycin, Spectinomycin, Gentamicin  **Recommended withdrawal time:** 3 to 14 days  **maximum residue limits:** |
| Fluoroquinolones | **Derivatives:** Enrofloxacin, Danofloxacin, Flumequine, Norfloxacin, Difloxacin  **Recommended withdrawal time:** 5 to 10 days  **maximum residue limits:** |
| Tetracyclines  Picture of Tetracycline 3D model | **Derivatives:** Chlortetracycline Oxytetracycline Doxycycline  **Recommended withdrawal time:** 5 days  **maximum residue limits:** |

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| **Antibiotic** | **Description** |
| Sulfonamides | **Derivatives:** Sulfacetamide, sulfamethoxypyridiazine, sulfamethoxydiazine, sulfamethoxazole, sulfadimidine, suflamethoxine, sulfadiazine, sulfafurazole.  **Recommended withdrawal time:** 5 days  **maximum residue limits:** |