Antimicrobial Stewardship Issue Brief

Importance to Elanco and our Stakeholders

Consumers want to understand how and where their food is produced, including what medicines are used to treat food animals and how that may impact human health. As a company dedicated to the health and welfare of animals, we have a responsibility to help answer these questions. Proper antimicrobial stewardship is critical for human health.

Background

Antimicrobial resistance (AMR) is an important public health concern. Elanco's approach to combating antimicrobial resistance aims to improve public health outcomes by reducing possible consumer exposure of pathogens through a range of solutions such as vaccines, parasite control, animal-only antimicrobials, animal nutrition, digital solutions, manufacturing controls, advocacy — and first and foremost, responsible use of medically important antimicrobials.

Elanco's leadership with food safety-focused vaccines is transforming science into public health solutions. For example, through our work to nearly eliminate salmonella in eggs and poultry, Elanco is offering advanced solutions to help prevent consumer exposure to salmonella and thereby reduce potential illness and the need for use of a medically important antimicrobials by humans.

The best way to reduce the need for antibiotic us is maintaining good health. Elanco utilizes a One Health concept, which considers a wide range of elements that contribute to the health of food animals and pets and how we may be able to support healthy outcomes for animals, as well as the people that rely on them for their livelihoods. Elanco will continue to advance antibiotic stewardship activities such as promoting responsible antibiotic use and reducing the need for medically important antimicrobials.

Elanco works closely with regulators and veterinarians to ensure – where infrastructure and regulations allow – medically important antimicrobials are used under professional supervision, to minimize the potential risk of resistance development that could compromise antibiotic use in human medicine. Our medically important antimicrobials are labeled only for the treatment of an established need in animals and only with veterinarian or similar professional oversight.

To further reduce the need for medically important antimicrobials to treat animal illness, Elanco is increasingly focused on disease prevention and early disease detection. Our vision is to move from treatment to prevention, by developing awareness programs and technologies that promote health and survivability even before an animal's life begins. Collectively, this can reduce animals' need for antibiotics, while promoting optimal animal welfare and food security.

Our Action

Antimicrobial stewardship has been an Elanco priority for more than two decades.

While we appreciate that antibiotics are critical, Elanco strongly supports the idea that they are just one of many tools available to maintain human and animal health and welfare. We're focused on finding solutions and alternatives to combat antimicrobial resistance – and to bringing greater clarity and collaboration to issues around antimicrobial stewardship.

We're working with leaders across industries and across the globe – including farmers, veterinarians, scientists and health care industry leaders – to develop long-term, responsible solutions. And we're actively engaged in shaping science-based recommendations on responsible antibiotic use, animal welfare and the long-term sustainability of the food system.

Internally, we're encouraging greater innovation to protect the long-term effectiveness of antibiotics. We've intentionally shifted our business to align with the following tiered approach to antimicrobial stewardship – positioning us to continue recognizing progress in this important, collaborative effort:

1. **Advance public health by preventing exposure to pathogens.** Elanco has pioneered highly effective and targeted vaccines to significantly reduce the likelihood of exposure to pathogens like salmonella. Preventing exposure to salmonella in eggs and poultry is a significant way that Elanco reduces the need for antibiotics in people.
2. **Reduce the need for antibiotics** – Farmers and veterinarians use many methods to keep animals healthy and prevent disease, including balanced diets for strong immune systems, well-maintained housing and good animal care. Elanco's industry-leading technical data, when combined with support from our technical experts, helps farmers make well-informed management decisions to support animal health and welfare.
3. **Replace antibiotics with alternatives** – Elanco has intentionally expanded our vaccine and nutritional health capabilities since 2015 to provide alternative solutions –including nutritional health products like enzymes, probiotics and prebiotics, parasiticides and vaccines. Eliminating the pathogen at the source reduces the need for antibiotic use in humans.
4. **Promote responsible antibiotic stewardship** – When therapeutic use of antibiotics is required, non-medically important (animal-only) antimicrobials are the preferred –and most responsible – first choice. These products were developed expressly for therapeutic use in animals and are not useful in human medicine. Their use does not create human health risk.
5. **Monitor the efficacy of antibiotics in livestock and pets** – Elanco has been an active participant in the monitoring of antibiotic susceptibility, as elaborated below.

6. **Actively engage and educate** – Elanco's Chief Medical Officer, Dr. Shabbir Simjee, provides regular training and information on AMR, participates in the development of global regulation and helps execute national AMR action plans across the globe.

Animal Health Strategy

As noted, "Preventing infections in the first instance is the best way to minimize the need for antimicrobials, as reducing the number of infections reduces the number of treatments needed. This approach is supported by the Animal Health Strategy, as it is fully in line with the principle promoted by the philosophy that prevention is better than cure. A reduction in the instance of animal disease and zoonotic infections should also minimize the need for, and use of, antimicrobials."[1]

The following measures help prevent disease and reduce the need for antimicrobials in all species:

1. Hygiene and biosecurity measures: hand washing, disinfection of facilities, quick removal of mortality and applying an "all in, all out" system
2. Improved husbandry: appropriate housing, ventilation and environmental conditions
3. Establishing production systems to avoid the need to buy and mix animal populations and prevent transportation of animals with unknown disease status
4. Avoiding animal stress
5. Implementing other zootechnical treatments to minimize disease and decrease use of antimicrobials
6. Introducing heard-specific health plans and prevention of prophylactic antibiotic administration
7. Implementing programs to control specific animal diseases (both viral and bacterial) by means of vaccination
8. Using scientifically proven, effective and safe alternatives to antimicrobials
9. Using only safe, high-quality feed and water
10. Providing incentives to farmers and encouraging them to adopt effective prevention measures to improve animal health and welfare standards and to monitor pathogens and their sensitivity at group level.

[1] Official Journal of the European Union, Directive C 299/20 (11.9.2015), Commission Notice – Guidelines for the Prudent Use of Antimicrobials in Veterinary Medicine, Section 6.1 (https://health.ec.europa.eu/system/files/2016-11/2015_prudent_use_guidelines_en_0.pdf)

Antimicrobial Stewardship Milestones

Through our pipeline, policies and advocacy efforts, Elanco seeks to protect the benefits of antibiotics in human medicine – while responsibly protecting the health and welfare of pets and farm animals and the safety of our food supply. We have made significant strides to advance antibiotic stewardship efforts globally:

Principles Toward Better Antimicrobial Stewardship

Antimicrobial resistance is a One Health issue impacting both human and animal medicine. We support the layers of protection in place to facilitate use of antibiotics in animals that pose minimal risk to human health. We work closely with regulators, veterinarians, animal health companies, farmers, pet owners, government and environmental health stakeholders as well as research and academic institutions to ensure – where allowed – antibiotics are used under strict professional supervision, to minimize the potential risk of resistance development.

Pet owners and farmers need innovation to address unmet health needs. Our aim is to prevent disease by supporting veterinarians and farmers with new and innovative products for disease prevention, survivability and early diagnosis of diseases. Our vision is to move from treatment to prevention, while championing awareness and technologies that promote health and survivability even before an animal's life begins. With increased knowledge and expanded access to data, a growing product portfolio and precision application, antibiotic alternatives such as vaccines, enzymes and probiotics are expected to contribute to more reliable and effective approaches.

Elanco's guiding principles for responsible antibiotic use include:

1. **Food chain stakeholder engagement:** Helping stakeholders across the food chain better understand and implement responsible antibiotic guidelines
2. **Global antibiotic classifications:** Considering international, national and regional ranking recommendations
3. **Disease treatment:** Supporting the administration of an antibiotic to an individual or a group of animals showing clinical signs of an infectious disease
4. **Disease control:** Supporting the administration of antibiotics for disease metaphylaxis/control in animals identified by a veterinarian
5. **Disease prevention:** Supporting the administration of antibiotics for disease prevention/ prophylaxis where determined by a veterinarian that animals are likely to get sick
6. **Utilization of risk assessment:** Following a risk assessment process, where regulations allow, to support the use of non-medically important antimicrobials for performance indications
7. **Concomitant use:** Supporting the approach that two medically important antibiotics of different classes should not be used at the same time, for the same disease indication (unless approved by the regulatory agency or supported by scientific evidence and/or veterinarian experience)
8. **Aquaculture:** Restricting use of antibiotics to areas where environmental exposure of the antibiotics can be sufficiently controlled, to avoid environmental impact or risk of resistance development
9. **Recording of antibiotic therapy:** Supporting veterinarian and/or farmer recordkeeping for antibiotic use in farm animals

With these principles, Elanco continues to build on international guidelines laid out by the World Organisation for Animal Health and Codex Alimentarius. Elanco is confident that these actions can meaningfully limit the risk from antibiotic resistance and protect sustainable animal production and pet health well into the future.

Healthy Animals and Safer, More Sustainable Food

Animal health is fundamental to animal welfare. Healthy animals are more efficient, helping to reduce the environmental footprint of livestock production. Elanco helps veterinarians and farmers deliver safe and healthy meat, milk and eggs to consumers by providing a wide portfolio of antibiotics – as well as alternatives such as vaccines, probiotics and nutritional solutions. We also offer services that enhance knowledge and decision-making for management practices and welfare standards. This comprehensive set of products and services helps our customers

mitigate diseases that directly impact animal health and welfare by controlling zoonotic bacteria that is important for public health and food safety.

A vital component of antimicrobial stewardship includes working to prevent the development of disease in the first place. As an example of our efforts, Elanco is a leader in the prevention of salmonella in poultry through our suite of vaccines This vaccine helps reduce transfer of the disease to humans, where it would be treated with an antibiotic. Preventing the issue reduces the potential need for antibiotic use in humans.

We recognize every farm operation is different. Most importantly, every animal is different. Advances in animal science, farming innovation and veterinary diagnostics allow practitioners to tailor health programs with a focus on preventing disease through better animal care practices, vaccination programs, nutrition and biosecurity. By understanding the needs of veterinarians and farmers and closely partnering with them, we can minimize and target how the antibiotic is used.

Antibiotic Resistance Monitoring

Antibiotic resistance monitoring is an essential component of responsible antibiotics use. Elanco has been part of the Centre Européen d'Etudes pour la Santé Animale (CEESA) antibiotic resistance monitoring program in the EU since its inception in 1998 and continues to take an active role in the organization's internationally recognized programs which monitor for trends in resistance that may impact the efficacy of treatments or the safety of food and gives early indications if any upward trends emerge. Elanco's Chief Medical Officer has been an active member of this CEESA program since 2004 and chaired the group's VetPath program for five years.

CEESA's AMR programs monitor the emergence of antibiotic resistance in foodborne pathogens as well as in pathogens that cause infections in farm and pet animals. Data from the program is used for risk assessments across the EU as well as in other geographies around the world. The programs also provide continued data on the efficacy of Elanco antibiotics, which can be used as an early indicator of emerging resistance profiles so usage patterns can be modified.

Over 20 years of CEESA data supports the findings that resistance in food-borne pathogens, as well as disease causing organisms, has remained low and stable across the EU. Elanco continues to work with the CEESA group making the data publicly available in a timely manner via peer reviewed publications as well as at international conferences in the form of oral publications and poster presentations.

In the United States, the Centers for Disease Control and Prevention tracks 18 major antibiotic resistance threats. Only two, campylobacter and non-typhoidal salmonella, are associated with animals. While antibiotic resistance to the primary treatments associated with animal agriculture remains low, the industry is committed to continued evaluation and improvement.

In New Zealand, we have an antibiogram program focused on bovine mastitis, the leading cause for antibiotic treatment in dairy cows. The program works by signing up dairy farms, collecting data from each farm, combining it with mastitis data from other farms, and developing a herd-level profile of mastitis pathogens, which is then shared with the treating veterinarians. These evidence-based insights help inform treatment plans by allowing veterinarians to select antibiotics that are most effective for the pathogens causing mastitis in a herd. The increased effectiveness of treatment decreases the amount of antibiotics required to treat infections, benefiting cows, dairies, and public health.

Governance and Risk Management

Our antimicrobial stewardship efforts are led by the joint efforts of our Executive Vice President of Innovation and Regulatory Affairs, as well as our Chief Medical Officer, who report twice per year to the Innovation, Science and Technology Committee of the Board of Directors.

The Innovation, Science and Technology Committee reviews the Company's regulatory strategy and compliance programs, as well as the competitive landscape in terms of related external scientific research, discoveries and commercial developments and potential future innovations in animal healthcare, as appropriate. The committee also assists the Board with oversight for enterprise risk management in areas affecting the Company's research and development efforts.

External Affiliations and Collaborations

Together with approximately 200 other companies and 700,000 veterinarians worldwide, Elanco undersigned the Health for Animals 2017 publication "Commitments and Actions on Antibiotic Use," which outlines key principles for responsible antibiotic use in the animal medicines industry Health for Animals publications are an excellent resource for research.
Following the World Health Organization 2015 Global Action Plan on Antimicrobial Resistance, countries around the world are requested to develop National Action Plans (NAPs) for reducing antimicrobial resistance. Elanco played an active role providing comments on draft NAPs as they were made available for public consultation.

Elanco also works with international institutions to conduct seminars and laboratory training on antibiotic resistance monitoring in compliance with current international standards. To date, Elanco has been involved in training across more than 20 countries and has trained over 500 laboratory and technical personnel.

We work closely with regulators and veterinarians to ensure, where appropriate, antibiotics are used under strict professional supervision and follow responsible use guidelines and principles. We also collaborate with key stakeholders across the value chain, including universities, global

health organizations, veterinary medicine professionals, and farm animal producers' associations in markets where Elanco commercializes antimicrobials.

Elanco supports reauthorizing the U.S. Animal Drug User Fee Act (ADUFA) to help increase veterinarian access to medicines. ADUFA supports the U.S. Food and Drug Administration (FDA) efforts to ensure new animal drug products are safe and effective for animals and that food from treated animals is safe. We also encourage countries to adopt the Codex Alimentarius international food standards to minimize the risk of antimicrobial resistance. The Codex Alimentarius Task Force on Antimicrobial Resistance recently updated guidance to reflect the best scientific knowledge and focus on policies that improve public health outcomes.

Clinical and Laboratory Standards Institute

Elanco is a founding and active member of the Clinical and Laboratory Standards Institute (CLSI) Veterinary Antimicrobial Susceptibility Subcommittee. The CLSI is responsible for establishing methods for testing antibiotic susceptibility, and for setting interpretive criteria which allow veterinarians to select the most appropriate antibiotics for treating sick animals. Elanco's Chief Medical Officer served as a voting member for a decade on this committee, and as co-chair for five years.

Metrics

Elanco has intentionally shifted our business away from medically important (shared-class) antibiotics and are focusing on non-medically important (animal-only) antibiotics and other types of medicines, which do not pose a risk to human antibiotic resistance, as well as antibiotic-free solutions. When Elanco began this journey in 2015, shared class antibiotics were 16% of revenue.

Antibiotics as a Percent of Total Company Revenue

	2018	2019	2020*	2021	2022	2023
Shared-class antibiotics (%)	12%	11%	12%	9%	8%	10%
Animal-only antibiotics & ionophores (%)	25%	24%	17%*	14%	15%	15%

* In August 2020, Elanco completed the acquisition of the animal health business of Bayer, increasing the total revenue of the company. The additional revenue was primarily in pet health but included shared-class antibiotics as well. These dynamics are important to consider when comparing the metric annually over the five-year window.

The content of this brief is informed by global ESG disclosure standards and frameworks.

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Definitions

Animal-only antibiotic: An antibiotic class that is prescribed for animal use only and does not have any human use

Antibiotic: Substance with a direct action on bacteria used for treatment or prevention of infections or infectious diseases (EPCEU). Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products.

Antibiotics resistance: The ability of micro-organisms to survive or to grow in the presence of a concentration of an antibiotic agent which is usually sufficient to inhibit or kill micro-organisms of the same species.

Antimicrobials: Substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoal (EPCEU. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products.

Antibiotic stewardship: The actions taken individually and as a profession to preserve the effectiveness and availability of antibiotic drugs through oversight and educated medical decision making while at the same time safeguarding animal, human, and environmental health

Antiparasitic: Substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with a repelling activity (EPCEU. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products.

Control/metaphylaxis: Administer an antibiotic agent to a group of animals containing sick animals and healthy animals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of the disease (https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/)

Indication: In medicine, a sign, symptom or medical condition that leads to the recommendation of a treatment, test or procedure

Medically important antibiotics: Antibiotic classes used in human medicine

Non-medically important antibiotics: Antibiotic classes not used in human medicine

One Health: An integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems – recognizing the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are intricately linked and interdependent.

Prevention/prophylaxis: Administer an antibiotic agent to an individual or a group of animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to

occur if the drug is not administered (https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/)

Resistance-transfer: The transfer of antibiotic resistance from one bacteria to another within or across host species.

Shared-class Antibiotic: An antibiotic that may be prescribed for animals, plants or humans.

Treatment: Administer an antibiotic agent to an individual or a group of animals showing clinical signs of an infectious disease (https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/)

Veterinarian: A person who is registered or licensed by the relevant veterinary statutory body of a country to practice veterinary medicine/science in that country (https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/)

Recent External Engagements

Talks

Simjee S. 2022. Global Progress on Antimicrobial Stewardship: Updates from The European Union. Animal Agriculture Alliance seminar on 'Emerging Issues Update: Responsible Antibiotic Use in Animal Agriculture. 28th March 2022.

Simjee S. 2022. The Urgent need to harmonise definition in the AMR space. Indian Association for the Advancement of Veterinary Research (IAAVR) 22nd Annual Conference. 9th April 2022. **(Invited Speaker)**

S Simjee. 2022. Updates from the EU on Antibiotic Policies. CONAFAB Conference. September 21-22, Guadalajara, Mexico.

S Simjee. 2022. Updates from the EU on Antibiotic Policies. Global Salmon Initiative. Madrid, Hyatt Centric Gran Via – Gran Vía, 31, Madrid 28013, Spain

S Simjee. Coffee Chat on Antibiotic Resistance and development of Antibiotic Alternatives. 7th Annual Animal Health, Nutrition and Technology Innovation Asia. October 18-19 Bangkok, Thailand.

Simjee S. 2022. Responsible use of antibiotics in Veterinary Medicine. WAAW Jakarta Indonesia 22nd November 2022. **(Invited Speaker by WOAH)**

Simjee S. 2022. Responsible use of antibiotics in Veterinary Medicine. WAAW South Africa 23rd November 2022. **(Invited Speaker by WOAH)**

Simjee S. 2023. Antibiotic Regulations to Address Sustainability. National Dairy Congress, Queretaro Mexico.

Simjee S, 2023. A Review of the Science Around Antimicrobial Resistance and Ionophore Coccidiostats. PVSG. Avila Spain.

Simjee S, 2023. AMR, from science to policy. AFMA Forum, Feed & Food The 4th Agricultural Revolution. 5-7 September. Sun City, South Africa.

Simjee S, 2023. AMR, from science to policy. 3rd Global Conference on Foodborne AMR (GCFA). 12-13 September, Seoul, South Korea.

Simjee S. 2023. Animal Agriculture Alliance Webinar on Responsible Antibiotic Use. 17 October.

Simjee S. 2023. European regulations on prevention use of antimicrobials in the EU – Regulations 2019/4 and 2019/6. AVAMS 2023, Surfers Paradise, Australia, 20-22 November.

Papers

Simjee S, Henninger M, Ippolito G and Atkinson J. 2022. Can we align antibiotic policies at an international level in the absence of harmonized definitions? Journal of Antimicrobial Chemotherapy, 77: 549–555. **https://doi.org/10.1093/jac/dkab465**

Trongjit S, Assavacheep P, Samngamnim S, My TH, An VTT, Simjee S and Chuanchuen R. 2022. Plasmid-mediated colistin resistance and ESBL production in *Escherichia coli* from clinically healthy and sick pigs. Nature Portfolio Scientific Reports 12:2466. **https://doi.org/10.1038/s41598-022-06415-0**

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Simjee S, and Ippolito G. 2022. European regulations on prevention use of antimicrobials from January 2022. *Brazilian Journal of Veterinary Medicine*, *44*, e000822. **https://doi.org/10.29374/2527-2179.bjvm000822**

Simjee S, Gould G, Maduro L, Boulianne M, Pridmore A and Parent E. 2023. No change in avilamycin (Surmax® Premix) minimum inhibitory concentration for *Clostridium perfringens* isolates recovered from poultry up to 7 years post-approval in Canada. *J Antimicrob Chemother* https://doi.org/10.1093/jac/dkad089

S. Simjee and G. Tice. 2023. The risk-benefit balance of resistance to ionophores in *Enterococcus faecium* and *Enterococcus faecalis* for ionophore coccidiostats in broiler chickens. Journal of Antimicrobial Chemotherapy, 78:9, 2121-2130. https://doi.org/10.1093/jac/dkad183

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pigs from different parts of Europe. *Journal of Applied Microbiology*, 2023, 134, 1–14 https://doi.org/10.1093/jambio/lxad132

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Simjee S, Sundram P, Mehrotra S. 2023. Do antibiotic residues in meat lead to antibiotic resistance in humans? Journal of Animal Husbandry Sciences and Technics, 294:31, 67-74

Posters

Parent E, Gould G, Farran J, Maduro L, Boulianne M and Simjee S. 2022. Minimal inhibitory concentrations of avilamycin to *Clostridium perfringens* isolates from broiler chicken farms before and after the approval of Surmax® Premix (Avilamycin) in Canada. American Veterinary Medical Association (AVMA)/American Association of Avian Pathology (AAAP) conference. Philadelphia, July 29-August 2, 2022

Simjee S, Power, W. 2022. Efficacy of florfenicol against *Staphylococcus pseudintermedius* recovered from dogs with otitis externa across the EU between 2017-2018. British Small Animal Veterinary Association Annual Conference. March 24-26, Manchester, UK.