Resisting Antimicrobial Resistance: Regulating the Use of Antibiotics in EU Animal Agriculture

RESEARCH NOTE #4 — Alice Di Concetto & Grace Martin

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Animal Law Europe, Bruxelles, 2022.

Alice Di Concetto,
Legal Advisor at The European Institute for Animal Law & Policy;

Grace Martin,
MChem, MSc

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Introduction

Animal agriculture, especially industrial farm animal production, has been a major driver of antimicrobial usage since the late 1940s. In Europe, the European Medicine Agency reported that of the 6,500 tonnes of antimicrobial veterinary medicinal products sold in 31 European countries in 2018, the vast majority (88%) accounted for the group treatment of animals. Animal agriculture accounts for a significant proportion of antimicrobial usage because industrial farm animal production methods keep animals in conditions that are conducive to making them sick.

In recent years, governmental bodies have taken notice of the significant health and environmental risks posed to animals and humans from routine, widespread antimicrobial usage in agriculture. In 2019, the EU vowed to restrict antimicrobial usage for preventive purposes, a regulatory framework which will go into effect in January of 2022. These new rules further restrict the use of antimicrobials for preventive purposes, and require that importers selling their products in the EU comply with the EU ban on the use of antimicrobials as growth promoters.

While this framework is a positive evolution, some significant shortcomings still exist in the way types of prohibited uses of antimicrobials are defined in the legislation. For instance, the new 2019/6 Regulation on Veterinary Medicinal Products prohibits the use of antimicrobials "to compensate for poor hygiene, inadequate animal husbandry, lack of care, or poor farm management." However, the regulation fails to specify or quantify what such poor standards would be. In the absence of a total ban on the preventive use of antimicrobials in animal agriculture, EU legislation still opens the door to a misuse of antimicrobials in animal agriculture.

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1. Antimicrobials in Animal Agriculture

1.1. Defining Antimicrobials

Antimicrobials are drugs such as antibiotics, antivirals, antifungals, and antiparasitics used to prevent and treat infections caused by pathogens (e.g., bacteria, viruses, fungi, and parasites) in humans, animals, and plants.[1]

EU law gives a similar regulatory definition: "'antimicrobial' means any substance with a direct action on microorganisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and antiprotozoals."[2]

Certain antimicrobials are for veterinary use only, whereas others are categorized as "shared-class" and are used in both animal and human medicine.[3] Among shared class antimicrobials, the World Health Organization (WHO) classifies antimicrobials for human use via three categories: important, highly important, and critically important antimicrobials.[4] An antimicrobial that is classified as critically important antimicrobials (CIAs) meets the following two criteria: it is the sole therapy (or one of limited available therapies) to treat serious bacterial infections in people, and it is a therapy used to treat infection caused by bacteria where there is a potential path for acquisition of resistance, either now or in the future.[5] CIAs are sub-divided into "High Priority" and "Highest Priority Critically Important Antibiotics.[6]

1.2. Use and Purposes of Antimicrobials in Animal Agriculture

1.2.1. THERAPEUTIC USE OF ANTIMICROBIALS

Therapeutic use, also called "metaphylactic use" refers to the use of antibiotics to treat disease that has been diagnosed by a licensed veterinarian.[7] This term refers to the treatment of specific illness, as opposed to non-therapeutic or prophylactic use. The treatment dose is typically very high and occurs for a short period of time.[8]

1.2.2. NON-THERAPEUTIC USES OF ANTIMICROBIALS

Antimicrobials can also be used for non-therapeutic purposes in farmed animals, which is any use "in the absence of microbial disease or known (documented) microbial disease exposure."[9]

1 World Health Organization, "Antimicrobial Resistance," https://www.who.int/health-topics/antimicrobial-resistance (last visited December 9th 2021).

2 Article 4(12), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/57 (2019).

3 FAIRR, Feeding Resistance: Antimicrobial Stewardship In The Animal Health Industry, 13 (2021)

4 World Health Organization, Critically Important Antimicrobials for Human Medicine, 6th Edition (2018), available online at: https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf.

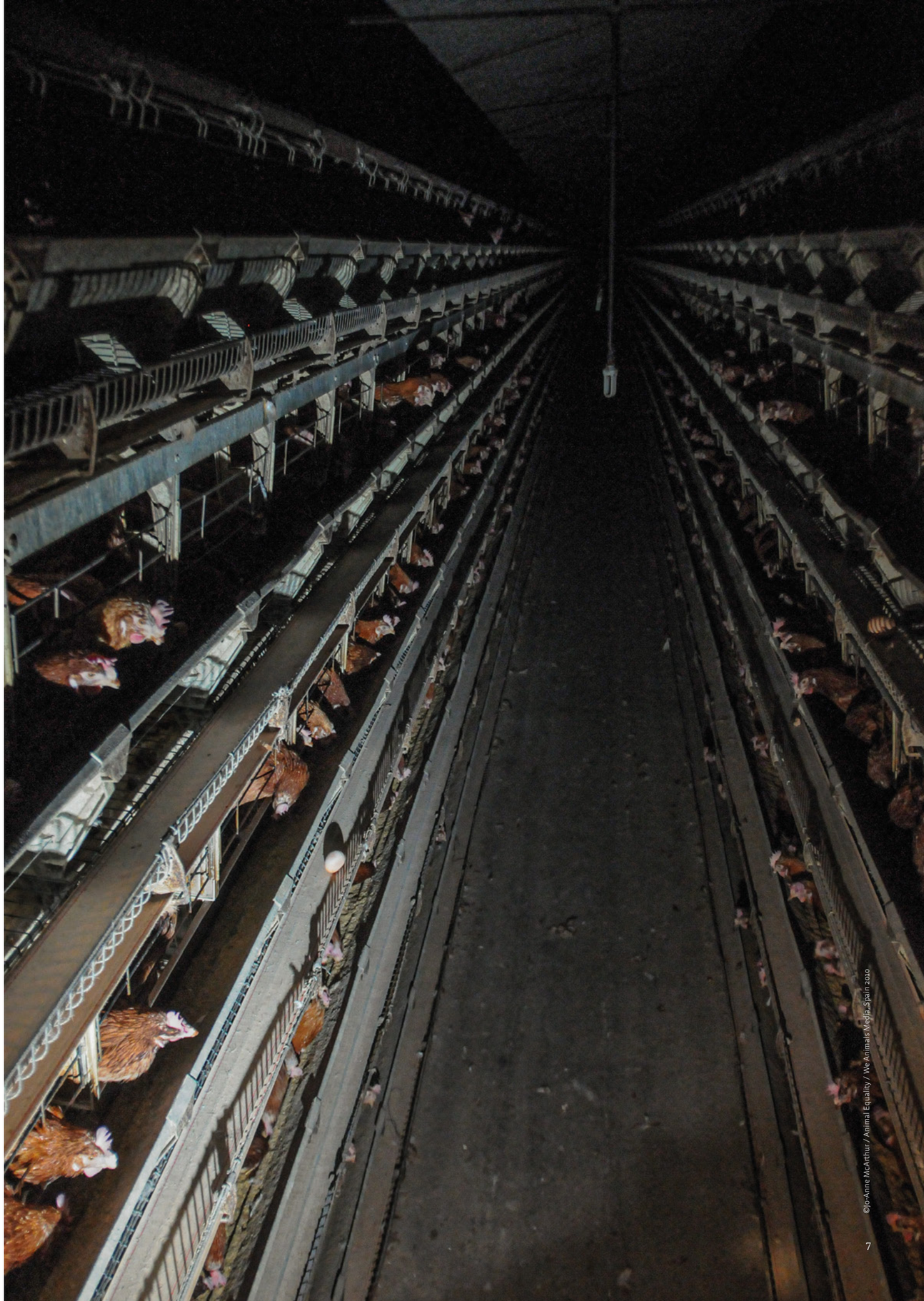
5 *Ibid*.

6 *Ibid*.

7 Article 4(15), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/57 (2019). *See also* The Pew Commission on Industrial Farm Animal Production, Putting Meat on the Table: Industrial Farm Animal Production in America, 63, (2008), available online: https://www.pewtrusts.org/en/research-and-analysis/reports/0001/01/01/putting-meat-on-the-table.

8 Compassion in World Farming, Antibiotics in Animal Farming: Public Health and Animal Welfare (2011), available online: https://www.ciwf.org.uk/media/3758863/Antibiotics-in-Animal-Farming-Public-Health-and-Animal-Welfare.pdf.

9 The Pew Commission on Industrial Farm Animal Production, Putting Meat on the Table: Industrial Farm Animal Production in America, 63, (2008), available online: https://www.pewtrusts.org/en/research-and-analysis/reports/0001/01/01/putting-meat-on-the-table.



Non-therapeutic use of antimicrobials pursues two main purposes:

- Preventive purposes (prophylaxis): the prophylactic use of antimicrobials is the administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection.[10] Antimicrobials for prophylactic purposes are usually administered at low dosage through drinking water or feed – called "medicated feed." Although allowed, prophylaxis is regulated under EU law, given its potentially significant contribution to antimicrobial resistance.
- Growth-promoting purposes: it is common practice on farms in many jurisdictions outside the EU to administer very low, subtherapeutic doses of antibiotics to animals through their feed to increase growth-rate and productivity, ensuring that the animals grow faster and bigger. This treatment is continuous and often occurs throughout an animal's entire lifespan. This non-therapeutic use is prohibited in the EU[11] but is still common in other jurisdictions such as the US and Canada.[12] However, the effectiveness of using antimicrobials in animal growth promotion appears to be diminishing, leading to an average weight gain in pigs of only a few per cent, compared with about 15% in 1980.[13] Although this non-therapeutic use is by name distinct from prophylaxis, the administration of antimicrobials for growth-promotion purposes has been shown to carry the ancillary benefit for producers of preventing infectious diseases in animals. Therefore, the distinction between preventive purposes and growth promotion is unclear.[14]

1.3. Benefits and Risks Posed by Antimicrobials Misuse in Animal Agriculture

The judicious use of antimicrobials can offer many benefits, starting with benefits to animals by ensuring their health. However, the routine use of antimicrobials in animal agriculture has contributed to the entrenchment of factory farming -- at great detriment to animal, human, and environmental health.

Scientists and policymakers have identified animal agriculture as a major driver of antimicrobial resistance in humans and animals due to the industry's over-reliance on the use of antimicrobials to produce high volumes of animal-source products. Both observational and randomized trials have shown a correlation between antibiotic use in animal agriculture and antibiotic resistance in humans.[15] A judicious use of antimicrobials is thus needed to outweigh the risks posed by perpetual and indiscriminate misuse by the industry in animal agriculture.

1.3.1. IMPORTANT BENEFITS OF ANTIMICROBIALS IN ANIMAL AGRICULTURE...

- **Animal Health Benefits**

  Antimicrobials can have health benefits for animals when used judiciously. For example, antimicrobials can protect animals from infections, and can treat infections, thereby limiting discomfort and stress.

10 Article 4(16), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/57 (2019).

11 Article 107(2), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/104 (2019).

12 The Pew Commission on Industrial Farm Animal Production, Putting Meat on the Table: Industrial Farm Animal Production in America (2008), available online: https://www.pewtrusts.org/en/research-and-analysis/reports/0001/01/01/putting-meat-on-the-table.

13 FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 11 (2021), K. Schoenmakers, How China Is Getting Its Farmers to Kick their Antibiotics Habit. Nature (2020); R. Laxminarayan, T. Van Boeckel, and A. Teillant, The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector, OECD (2015).

14 Compassion in World Farming, Antibiotics in Animal Farming: Public Health and Animal Welfare (2011), available online: https://www.ciwf.org.uk/media/3758863/Antibiotics-in-Animal-Farming-Public-Health-and-Animal-Welfare.pdf.

15 T.F. Landers, T. F., B. Cohen, T. E. Wittum, and E. L. Larson, A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential, Public Health Reports (2012).

16 *Ibid.*

17 *Ibid.*

18 *Ibid.*

19 *See* for instance in France: Autorité de la concurrence, "The Autorité Hands Out Fines Worth 93 Million Euros to a Cartel in the Ham and Cold Meats (Charcuterie) Sector," July 16th 2020 https://www.autoritedelaconcurrence.fr/en/press-release/autorite-hands-out-fines-worth-93-million-euros-cartel-ham-and-cold-meats-charcuterie (last visited December 10th 2021). For a more detailed analysis of the consequences of vertical integration on farmers' livelihood and of consolidation on consumer's purchasing power in the US, *see* the work of Christopher Leonard.

20 Article 4(11), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/ 57 (2019).

21 European Medicines Agency, "Antimicrobial Resistance," https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/antimicrobial-resistance (last visited December 10th 2021).

22 World Health Organization, "Antimicrobial Resistance," https://www.who.int/health-topics/antimicrobial-resistance (last visited December 9th 2021).

23 The Pew Commission on Industrial Farm Animal Production, Putting Meat on the Table: Industrial Farm Animal Production in America, 16, (2008), available online: https://www.pewtrusts.org/en/research-and-analysis/reports/0001/01/01/putting-meat-on-the-table, M. Nüesch-Inderbinen and R. Stephan, Epidemiology of Extended-Spectrum β-Lactamase-Producing *Escherichia coli* in the Human-Livestock Environment, Current Clinical Microbiology Reports (2016) ; Rafael Grossi Botelho, Sérgio Henrique Monteiro and Valdemar Luiz Tornisielo, Veterinary Antibiotics in the Environment in Emerging Pollutants in the Environment – Current and Further Implications (Marcelo L. Larramendy, ed.) (2015) ; United Nations Environment Programme, Emerging Issues of Environmental Concern, Frontiers (2017) ; P.-Y. Hong *et al.*, Environmental and Public Health Implications of Water Reuse: Antibiotics, Antibiotic Resistant Bacteria, and Antibiotic Resistance Genes. Antibiotics (2013).

However, industrial animal producers liberally use antimicrobials to ensure the functioning of their systemically abusive production methods. Often, this means using antimicrobials to keep ill or suffering animals alive when they would have otherwise died due to poor animal welfare and unsanitary conditions.

- **Human Health Benefits**

  The judicious use of antimicrobials can further safeguard producers and consumers by mitigating infection risks on farms and in animal-source products.[16] However, many claims about human benefit from antibiotic usage in animal agriculture have not been fully demonstrated.[17]

  Furthermore, because antibiotics enable the prevention and treatment of infections, and have the effect of promoting fast growth in animals, their use has been instrumental in making animal-source food affordable and in ensuring farmers' livelihoods.[18] For the past two decades though, these economic benefits for farmers and consumers have largely been undermined by the extreme consolidation at play in animal agriculture production in Europe, which in turn has contributed to impoverishing farmers and fixed retail pricing.[19]

1.3.2. ...FOR A POTENTIALLY EVEN GREATER RISK: ANTIMICROBIAL RESISTANCE

- **Antimicrobial Resistance**

  The overuse of antimicrobials has given rise to antimicrobial resistance, which poses significant risks to public health and ecosystems. EU law defines antimicrobial resistance as "the ability of microorganisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill microorganisms of the same species."[20] In other words, antimicrobial resistance is a phenomenon whereby microorganisms (bacteria, fungi, parasites, and viruses) become partially or fully resistant to antimicrobial drugs, such as antibiotics, antifungal, antiprotozoal, and antivirals that had once been effective treatments.[21] With such resistance to medicines, infections become increasingly difficult and, in some cases, impossible to treat.

  Although antimicrobial resistance occurs naturally, the overuse (i.e. using too much) and misuse (i.e. using in a manner or dose other than prescribed) of antimicrobials greatly hastens the rate at which they become ineffective against infection.[22] Antimicrobial resistance is furthermore exacerbated by the many points of animal, human, and plant exposure to antimicrobials and antimicrobial resistant pathogens.[23]

Direct contacts with antimicrobials and antimicrobial-resistant pathogens	**Indirect contacts with antimicrobials antimicrobials-resistant pathogens**
-During drug manufacturing. -The disposal of unused antibiotics, and also via the use and application of waste material containing these antibiotics. -Misuse and overuse of drugs on farms	-From contaminated water, soil, and air as a result of leaks occurring from antimicrobials manufacturing plant, from farms, from manure of farmed animals treated with antimicrobials.[24]
-From animals on farms[25], during transport, and in slaughterhouses.	-From animal source products, due to antibiotics residues when withdrawal periods were not respected. -From non-animal source products when crops, such as fruit and vegetables or grains, have been applied manure of farmed animals treated with antimicrobials.

In 2015, the European Center for Disease Prevention and Control estimated that 33,000 people die every year due to antibiotic resistant infections.[26] In 2014, the WHO estimated that many major bacteria groups such as *E. Coli, K. Pneumonia*, and *S. Aureus* around the world are now resistant to antimicrobial treatment in 50% of the cases.[27]

- **Environmental Impacts of Antimicrobial Resistance**

  The overuse of antibiotics in animal agriculture has a multitude of negative impacts on animals, humans, plants, and ecosystems depending on the many different routes antimicrobials and resistant pathogens take, beyond transmission through the food chain. For instance, antibiotic-resistant bacteria that have originated from farmed animals can be detected in the environment surrounding animal farming operations, in meat products in stores, and in humans themselves.[28]

  Given the adverse impacts of antimicrobial leaks on the waterways, animals, plants, and soils,[29] EU law treats antibiotics as pollutants.[30]

- **Economic Impacts of Antimicrobial Resistance**

  The WHO estimates that antimicrobial resistance contributes to increased hospital stays and higher medical costs, with significant financial impacts on families, society, and health systems.[31] The World Bank forecasts that antimicrobial resistance will hamper global Growth Domestic Product by 1.1% to 3.8% by the year 2050.[32] This forecast includes significant impacts to livestock production – with an 11% loss expected in low-income countries, greatly affecting the livelihoods of those living there.[33] Finally, the overuse and misuse of antibiotics heavily affects the revenue of animal health companies and their investors.[34]

24 FAIRR, Feeding Resistance: Antimicrobial Stewardship In The Animal Health Industry, 12 (2021).

25 S.B. Levy, G.B. FitxGerald, A.B. Macone, Changes in Intestinal Flora of Farm Personnel After Introduction of A Tetracycline-Supplemented Feed on a Farm, New England Journal of Medicine (1976) ; C. Chen and F. Wu, Livestock-Associated Methicillin-Resistant Staphylococcus Aureus (LA-MRSA) Colonization and Infection Among Livestock Workers and Veterinarians: A Systematic Review and Meta-Analysis, available at SSRN 3208968 (2018); M. Nadimpalli, *et al.*, Persistence of Livestock-Associated Antibiotic-Resistant *Staphylococcus Aureus* Among Industrial Hog Operation Workers In North Carolina Over 14 Days, Occup Environ Med. (2015).

26 European Center for Disease Prevention and Control, "33 000 People Die Every Year Due to Infections with Antibiotic-Resistant Bacteria, https://www.ecdc.europa.eu/en/news-events/33000-people-die-every-year-due-infections-antibiotic-resistant-bacteria (last visited December 12th, 2021).

27 World Health Organization, Antimicrobial Resistance Global Report on Surveillance: 2014 summary, 4 (2014).

28 FAIRR, Feeding Resistance: Antimicrobial Stewardship In The Animal Health Industry, 13 (2021).

29 J. L. Martinez, Environmental Pollution by Antibiotics and by Antibiotic Resistance Determinants, Environmental Pollution (2009); C. Ding and J. He, Effect of Antibiotics in the Environment on Microbial Populations, Applied Microbiology and Biotechnology (2010).

30 Annex III, Regulation (EU) 2019/4.

31 World Health Organization, "Antibiotic Resistance," https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance (last visited December 9th 2021).

32 FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 11 (2021).

33 World Bank Drug-Resistant Infections: A Threat to Our Economic Future, available online: https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf (2017).

34 FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry (2021).

35 *See* FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry (2021).

36 U.S. Food and Drug Administration, Guidance for Industry #209, April 2013 (U.S.A.), available online: https://www.fda.gov/media/83488/download.

37 Article 105(2) et (3), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/ 57 (2019).

38 American Veterinary Medical Association, "Judicious Therapeutic Use of Antimicrobials," https://www.avma.org/resources-tools/avma-policies/judicious-therapeutic-use-antimicrobials (last visited December 10th 2021).

39 *Ibid.*

40 *Ibid.*

41 Four Paws International, Guidance Document to Support the Implementation of the New EU Regulations on Veterinary Medicinal Products and Medicated Feed through Higher Animal Welfare (2021)

42 American Veterinary Medical Association, "Judicious Therapeutic Use of Antimicrobials," https://www.avma.org/resources-tools/avma-policies/judicious-therapeutic-use-antimicrobials (last visited December 10th 2021).

43 *Ibid.*

44 *Ibid.*

1.3.3. THE NEED FOR JUDICIOUS USE OF ANTIMICROBIALS

In response to antimicrobial misuse in animal agriculture, international organizations such as the EU, the WHO, and the World Animal Health organization (OIE) have called for a "judicious" or "cautious" or "prudent" use of antimicrobials, and more generally, "antimicrobial stewardship."[35] General rules of the use of antimicrobials include:

- Limiting such drugs to uses in farmed animals that include veterinary oversight.[36]
- Antimicrobials should be administered only after a preliminary diagnosis or a proper assessment of the health status of the animal(s)[37] which indicates that antimicrobial therapy is appropriate. [38]
- Culture and antimicrobial susceptibility testing should be performed when possible to guide the selection of antimicrobials.[39]
- Antimicrobial therapy for uncomplicated viral infections and non-septic inflammatory conditions should be avoided.[40]
- Antimicrobial therapy should be targeted to ill or at-risk animals when possible, and other management strategies, such as improved animal welfare levels,[41] should be used to prevent infection in healthy individuals.[42]
- Accurate records of therapy and outcome should be maintained.[43]
- Environmental contamination with antimicrobials must be avoided whenever possible.[44]

2. Industrial Farm Animal Production as a Major Driver of Antimicrobials Use

2.1. The Origins of Antimicrobial Usage on Industrial Farms

Agricultural producers have understood the commercial benefits of extreme confinement of animals since the start of the industrial revolution. However, early attempts to concentrate animal agriculture failed due to the spread of infections from unsanitary conditions. The Swill Milk Scandal in New York state in the 1850s – which reportedly led to the deaths of some 8,000 infants – is an example of a disastrous early attempt to concentrate dairy cows.[45]

It was not until the late 1940s, with innovations in biotechnology, and specifically in veterinary medicine through the use of antibiotics, and animal nutrition with the use of feed additives, that animal agriculture producers were able to increase their productivity by confining animals in levels of extreme density. In that sense, the history of antimicrobials in animal agriculture is closely linked to the history of industrial farm animal production, with such medical agents enabling factory farming to proliferate.

The history of agricultural antibiotics began with synthetic sulphonamides in 1935, when Bayer marketed Prontosil (sulfochrysoidine), the first effective drug against Gram-positive infections.[46] In Britain, sulphonamides, particularly Prontosil, were marketed for use in animals from 1938 onwards. Intramammary preparations of penicillin were used to treat bovine mastitis.[47] Farmers used this to "purify" milk to guarantee food safety. Later, concern shifted from the bacterial load of the product to the antibiotic residues in the milk.[48]

In addition to treating and preventing infections in animals, the poultry industry later discovered in the 1940s that feeding subtherapeutic levels of particular antibiotics resulted in more rapid animal growth.[49] Further studies on livestock species confirmed increased growth as a result of routine administration of sub-therapeutic antimicrobial levels.[50] In 1948, Merck's sulfaquinoxaline was the first antibiotic to be officially licensed for routine inclusion in poultry feed against coccidiosis.[51] The same year, Merck announced the discovery of vitamin B12, which was also found to have antimicrobial and growth-promoting properties.

By the mid-1950s, antibiotic use also proliferated to other areas of US food production beyond livestock production, such as crop production, commercial beehives, and farmed fish.[52]

45 The New York Times, «Swill - Milk and Infant Mortality», May 22, 1858, https://www.nytimes.com/1858/05/22/archives/swill-milk-and-infant-mortality.html (last visited December 10th 2021).

46 C. Kirchhelle, Pharming animals: A Global History of Antibiotics in Food Production (1935–2017), Nature (2018).

47 R. Gustafson and R. Bowen, Antibiotic Use in Animal Agriculture Journal of Applied Microbiology (1997).

48 K. Smith-Howard, Antibiotics and Agricultural Change: Purifying Milk and Protecting Health in the Postwar Era, Agricultural History (2010).

49 The Pew Commission on Industrial Farm Animal Production, Putting Meat on the Table: Industrial Farm Animal Production in America, 15, (2008), available online: https://www.pewtrusts.org/en/research-and-analysis/reports/0001/01/01/putting-meat-on-the-table.

50 C. Kirchhelle, Pharming Animals: A Global History of Antibiotics in Food Production (1935–2017), Nature (2018).

51 W.C. Campbell, History of the Discovery of Sulfaquinoxaline as a Coccidiostat, The Journal of Parasitology (2008).

52 *Ibid.*

Today, aquaculture is a sector of animal agriculture where the use of antimicrobials is expanding rapidly, on account of the industrialization of fish and shrimp farming[53] and the resulting growth of several bacterial diseases on aqua farms.[54] Producers of the five most farmed aquatic species in aquaculture commonly use classes of antimicrobials that are listed as critically important and highly important for human medicine by the WHO.[55]

2.2. The Animal Health Industry

The animal health industry's market value is estimated to be $47.1 billion, with farm animal health representing 62% of its total market value.[56] Following mergers and acquisitions, the animal health industry has undergone significant concentration. In as little as 12 years, the four biggest publicly-traded animal health companies – Zoetis, Elanco, Boehringer Ingelheim, and Merck/MSD – increased their market share by more than ten percent, jumping from under 30% to over 40%.[57]

In 2019, the animal health sector spent more than $3.2 million in lobbying expenditures in the US and the EU.[58] The four biggest publicly-traded animal health companies in the world – Zoetis, Elanco, Boehringer Ingelheim, and Merck/MSD – are represented by Animal Health Europe in the EU institutions,[59] in addition to their own respective lobbying activity in Brussels.[60] These groups regularly lobby the EU institutions on matters pertaining to the regulation of antimicrobials, even though official data does not disclose the details of their recommendations.[61]

2.3. Antimicrobials Misuse on Farms: A Global Phenomenon

2.3.1. IN EUROPE

In Europe, the import of US breeds and antibiotic use facilitated the emergence of factory farming, starting with poultry production in cages shortly after the end of World War II. At the time, unlike the US, only antimicrobials under the form of premixed antibiotic solutions and medicated feed were available for sale over the counter. Certain antimicrobials for growth promotion purposes were marketed without veterinary prescription in West Germany (1951), Britain (1953), the Netherlands (1954), and in France (1955).[62] By 1958, an estimated 50% of British pigs were fed antibiotics and nearly all unweaned piglets had access to tetracycline-supplemented feed. In the mid-sixties, West Germany's Minister of Agriculture estimated that 80% of mixed feeds for young pigs, veal calves, and poultry contained antibiotic additives.[63]

In the 1950s, the whaling industry also started using antimicrobials to fight bacterial spoilage and to mitigate infection risks during long processing times.[64]

53 K. Holmström, Antibiotic Use in Shrimp Farming and Implications for Environmental Impacts and Human Health, International Journal of Food Sciences and Technology (2003).

54 R. C. Okocha *et al.*, Food Safety Impact of Antimicrobial Use and their Residues in Aquaculture, 5 Public Health Reviews (2018).

55 D. Schar *et al.*, Global Trends in Antimicrobial Use in Aquaculture, 4, Nature (2020).

56 FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 19 (2021).

57 29.3% in 2007 to 42.6% in 2019. Four-firm concentration ratio calculated based on FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 20 (2021).

58 FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 63 (2021).

59 Animal Health Europe, 2020 Annual Report (2020), available online: https://annual-report.animalhealtheurope.eu/.

60 Data retrieved from LobbyFact.eu based on the European Commission's Transparency Register.

61 *Ibid.* and FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 63 (2021).

62 C. Kirchhelle, Pharming Animals: A Global History of Antibiotics in Food Production (1935–2017), Nature (2018).

63 *Ibid.*

64 *Ibid.*

65 Animal Health Europe, Key Figures (2020), available online: https://annual-report.animalhealtheurope.eu/wp-content/uploads/2021/01/2020-annual-report.pdf ; Claudio D. Miranda, Current Status of the Use of Antibiotics and the Antimicrobial Resistance in the Chilean Salmon Farms, 3 Frontiers in Microbiology (2018).

66 S. J. More, European Perspectives on Efforts to Reduce Antimicrobial Usage in Food Animal Production, 3 Irish Veterinary Journal (2020).

67 European Medicines Agency, Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2019 and 2020 Trends from 2010 to 2020, 11th ESVAC report (2021), available online: https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf.

68 S. J. More, European Perspectives on Efforts to Reduce Antimicrobial Usage in Food Animal Production, 3 Irish Veterinary Journal (2020).

69 Commission Implementing Decision 2013/652 of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria, O.J. L 303 (2013) (now replaced by Commission Implementing Decision (EU) 2020/1729 of 17 November 2020 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria and repealing Implementing Decision 2013/652/EU, O.J. L 387 (2020)).

70 European Commission, A European One Health Action Plan Against Antimicrobial Resistance (AMR), 6 (2017).

71 European Commission, Progress Report on the EU's AMR Action (2020), available online: https://ec.europa.eu/health/sites/default/files/antimicrobial_resistance/docs/amr_2018-2022_actionplan_progressreport_en.pdf.

72 C. Kirchhelle, Pharming Animals: A Global History of Antibiotics in Food Production (1935–2017), Nature (2018).

73 *Ibid.*

In aquaculture, the salmon industry in Norway was formerly a major consumer of antibiotics until the introduction of vaccines against furunculosis and vibriosis pathologies, which reduced the need to use antibiotics in Norwegian aquaculture by 99% between 2003 and 2014.[65]

Regulatory efforts to reduce antimicrobial usage in animal agriculture began in the late 1990s and have been intensifying since the late 2010s (see infra). In addition to reducing the use of antimicrobials, EU law and policy has focused on monitoring antimicrobial usage in animal agriculture.

In 2009, the European Medicine Agency (EMA) created the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) to harmonize the collection and reporting of antimicrobial usage in animals. ESVAC publishes detailed usage trends in European countries based on sales data.[66] The latest ESVAC report, published in November of 2021, shows that the volume of antimicrobials sold for use in food-producing animals in Europe fell by more than 43% between 2011 and 2020.[67]

In addition to the ESVAC reports, the European Food Safety Authority and the European Center for Disease Prevention and Control jointly publish a yearly summary report on antimicrobial resistance in animal agriculture.[68] The 2013/652 Implementing Decision[69] facilitated such reporting by harmonizing antimicrobial resistance monitoring programs conducted via samples collected from farmed animals.

Following WHO's adoption of its Global Action Plan Against Antimicrobial Resistance, the EU further presented a series of policy measures and reforms in its 2017 "AMR Action Plan," which support pre-existing initiatives.[70] This Plan pursues three main goals:[71]

- An accelerated reduction of antimicrobial use, including the promotion of the prudent use of antimicrobials in animal agriculture through the enactment of new legislation.
- Investment in the research and development of alternatives to antimicrobials, such as the development of new vaccines for humans and animals.
- The intensification of cooperation efforts with non EU-countries to reduce antimicrobials globally, including through the adoption of rules on antimicrobial usage in trade agreements with third countries.

2.3.2. IN THE REST OF THE WORLD

Therapeutic and nontherapeutic antibiotic use also spread to other countries. For example, Japan started licensing antimicrobial feed additives in 1953 and increased its dependence on the use of antimicrobial livestock and fish production, exacerbated by limited land availability.[72] Another country to adopt widespread use of antimicrobials is China, where the introduction of liberal economic policies in the 1980s prompted the settlement of large US and Thai corporations relying on the routine use of antimicrobials on their intensive poultry operations.[73]

Today, antimicrobial use remains high in animal agriculture due to the increased demand for animal protein in low- and middle-income countries. For instance, the global agricultural usage of antimicrobials is estimated to increase by 67% from 2010 to 2030, largely from rising usage in Brazil, Russia, India, and China.[74] Chile is another country where the use of antimicrobials of critical importance to human health has boomed on account of the industrialization of its salmon industry.[75]

2.3.3. GLOBAL POLICY EFFORTS TO COMBAT ANTIMICROBIAL RESISTANCE

Following the United Nations' Political Declaration on Antimicrobial Resistance (AMR) in 2016,[76]the WHO adopted its Global Action Plan on AMR. The World Animal Health Organization (OIE)[77] and the UN's Food and Agriculture Organization also adopted the WHO Action Plan, with the OIE adopting its own Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials in 2016.[78] This plan mainly aims to encourage cooperation between nations to "optimize the use of antimicrobial medicines in human and animal health" among other measures.[79] All these efforts are also based on the "One Health" concept, developed by the scientific community in 2004, which identifies the synergies between optimal health for people, animals, and the environment.[80]

The new EU legislation regulating the use of antimicrobials in animal agriculture also produces extra-territorial effects by requiring that imported animal source food products comply with EU standards. These standards include the prohibition on the use of antimicrobials as growth promoters, restrictions on the prophylactic use of antimicrobials on farms, and the residue limits in animal-source products (see infra). Failure to meet these standards can result in the issuance of bans on imports from third countries to the EU. One example is the temporary ban on the imports of contaminated prawns from China issued in 2002 and Bangladesh in 2008.[81]

74 Van Boeckel *et al.*, Global Trends in Antimicrobial Resistance in Animals in Low- and Middle-Income Countries, Science (2019).

75 Claudio D. Miranda, Current Status of the Use of Antibiotics and the Antimicrobial Resistance in the Chilean Salmon Farms, 3 Frontiers in Microbiology (2018).

76 United Nations, Political Declaration of the High Level Meeting of the General Assembly on Antimicrobial Resistance (2016) available online: https://digitallibrary.un.org/record/842813?ln=en.

77 World Health Organisation, Global Action Plan on Antimicrobial Resistance (2015), available online: https://www.who.int/publications/i/item/9789241509763.

78 World Organisation for Animal Health (OIE), The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials (2016), available online: https://www.oie.int/app/uploads/2021/03/en-oie-amrstrategy.pdf.

79 World Health Organization, Global Action on Antimicrobials, 10 (2015), available online: https://www.amcra.be/swfiles/files/WHO%20actieplan_90.pdf.

80 *See* D. Destoumieux-Garzón *et al.*, The One Health Concept: 10 Years Old and a Long Road Ahead, Frontiers Veterinary Science (2018); John S. Mackenzie, and M. Jeggo, The One Health Approach – Why Is It So Important?, Tropical Medicine and Infectious Disease (2019).

81 R. Lulijwa *et al.*, Antibiotic Use in Aquaculture, Policies and Regulation, Health and Environmental Risk: A Review of the Top 15 Major Producers, 654, Reviews in Aquaculture (2020).

© A farm owner picks up dead chicks from the barn floor, Jo-Anne McArthur / Animal Equality / We Animals Media, Spain 2020.

3. The Regulation of Antimicrobials Use in EU Animal Agriculture

3.1. Legislative History

Regulatory efforts to reduce the use of antimicrobials in animal agriculture date back from the late 1990s, when the European Union adopted a ban on a series of antimicrobials in animal agriculture used as growth promoters.[82] The first to be banned was avoparcin, an antimicrobial widely used in feed for chickens, pigs, calves, cows, and lambs due to its positive effects on animal growth.[83] It was not until 2006 that the EU prohibited the use of the remaining four antimicrobials used as growth promoters, thereby banning the practice of using antimicrobials for growth-promoting purposes.[84] In 2017, the EU Legislature further imposed limits on antimicrobial residue in food products, limits which pertain to 57 antimicrobial substances.[85]

In 2019, the EU Legislature revamped its regulatory framework to further restrict the prophylactic use of antimicrobials and extend the ban on the use of antimicrobials as growth promoters to imported products. The new regulations 2019/4 on medicated feed[86] (the Medicated Feed Regulation) and 2019/6 on veterinary medicinal products (the Veterinary Medicinal Product Regulation)[87] thus form the new regulatory framework for the use of medication in animal agriculture in the EU. Both texts amend previous legislative acts[88] and will enter into force on January 28th 2022. In achieving these overarching policy goals, the Medicated Feed and the Veterinary Medicinal Product Regulations primarily strengthen, update, and harmonize rules on the production, marketing, sales, and administration of medicines with a view to reduce their use in animal agriculture and limit antimicrobial resistance.

3.2. The New Regulatory Framework

3.2.1. THE NEW EU LEGISLATION[89]

- **The Veterinary Medicinal Products Regulation**

  The Veterinary Medicinal Products Regulation covers veterinary medicinal products, defined as "any substance and or combination of substances which fulfils at least one of the following conditions:

a. It is presented as having properties for treating or preventing disease in animals;

b. Its purpose is to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;

c. Its purpose is to be used in animals with a view to making a medical diagnosis;

d. Its purpose is to be used for euthanasia of animals."[90]

82 These substances were bacitracin zinc, spiramycin, virginiamycin, and tylosin phosphate. Council Regulation (EC) No 2821/98 of 17 December 1998 amending, as regards withdrawal of the authorisation of certain antibiotics, Directive 70/524/EEC concerning additives in feedingstuffs, OJ L 351 / 4 - 8 (1998).

83 Commission Directive 97/6/EC of 30 January 1997 amending Council Directive 70/524/EEC concerning additives in feedingstuffs, O. J. L 35 / 11 - 13 (1997). *See also* FAIRR, Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry, 36 - 37 (2021) and M. Casewell *et al.*, The European Ban on Growth-Promoting Antibiotics and Emerging Consequences for Human and Animal Health, Journal of Antimicrobial Chemotherapy (2003).

84 These substances were: monensin sodium, salinomycin sodium, avilamycin, and flavophospholipol. Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition, OJ L 268 /29 - 43 (2003).

85 Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin OJ L 15/ 1 - 72 (2010).

86 Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC, O.J. L 4/1 – 23 (2019).

87 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/ 43–167 (2019).

88 Regulation 2019/4 on medicated feed amends Regulation 183/2005 laying down requirements for feed hygiene (O.J. L 35/ 1 – 22 (2005) and repeals Directive 90/167/EEC laying down the conditions governing the preparation, placing on the market and use of medicated feedingstuffs in the Community (O.J. L 92/ 42 – 48 (1990), while Regulation 2019/6 on veterinary medicinal products repeals Directive 2001/82/EC on the Community code relating to veterinary medicinal products O.J. L 311/1 – 66 (2001).

89 This section includes excerpts of a Guideline document on the new EU regulatory framework for antibiotics use co-authored by Alice Di Concetto for Four Paws International: Four Paws International, Guideline Document on Antimicrobials Use, Four Paws International, forthcoming.

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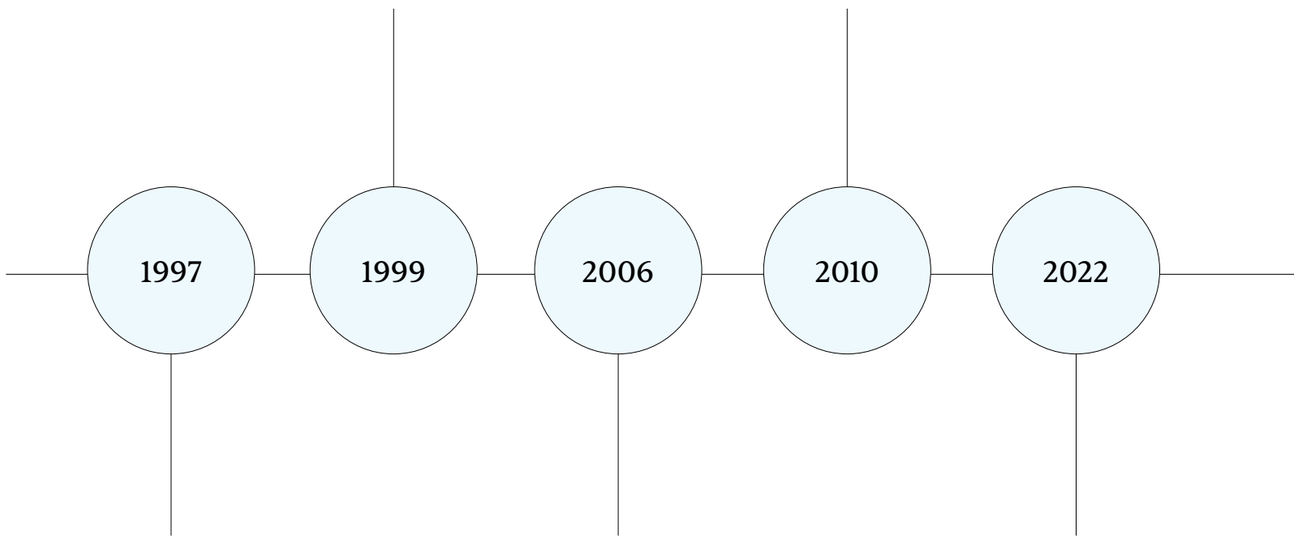
Timeline of regulatory efforts to reduce antimicrobial use in EU animal agriculture:



The Regulation also applies to active substances used as ingredients and inactivated immunological veterinary medicinal products.[91] Finally, some provisions in the regulation also apply to veterinary medicinal products prepared in a pharmacy.[92] The scope excludes medicated feed, which is covered in the Medicated Feed Regulation, and which is not subject to a marketing authorization.

- **The Medicated Feed Regulation**

The Medicated Feed Regulation applies to animal feed mixed with medicine.[93]

The Medicated Feed Regulation regulates the manufacturing, storage, and transport of medicated feed, as well as the commercialization of medicated feed and its ingredients[94] ("intermediate products").[95] Furthermore, the Medicated Feed Regulation applies to all medicated feed manufactured, stored, transported, and placed on the EU markets – including when such feed is intended to be exported outside the EU.[96]

- **Main Provisions**

- *Marketing Authorization*

The Veterinary Medicinal Products Regulation requires that all products included in its scope should obtain a marketing authorization.[97]

- *Production*

All businesses involved in the manufacturing, storage, and transport of veterinary medical products and medicated feed must obtain an agreement from the competent authorities of the Member States in which they operate.[98] Member States must further keep a record of all the approved operators.[99]

- *Commercialization*

Both regulations also require that all products should be labeled " in a simple, clear, and easily understandable manner for the end users."[100] Among other requirements, the product should carry a label that identifies the active substances of the products and the expiration date. The labelling of medicated feed should further indicate counter-indications, as well as information regarding proper disposal and that the product threatens the environment and may contribute to antimicrobial resistance.[101]

- *Advertising*

Both acts strictly limit the advertising of veterinary medicinal products and medicated feed. Advertising for veterinary medicinal products subject to prescription must be directed to veterinarians only.[102] The distribution of promotional samples of products containing antimicrobials is prohibited.[103]

- *Restriction on the Use of Antimicrobials in Animal Agriculture*

The **Veterinary Medicinal Products Regulation** imposes specific, additional rules regulating the use of antimicrobials – as opposed to medicinal products[104] and immunological veterinary products.[105]

90 Article 2 and 4, Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/ 55 - 56 (2019).

91 Articles 2((2) and 6, *Ibid*.

92 Article (2)(6)(b) and (c) *Ibid*.

93 Article 3(2)(a), Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC, O.J. L 4/1 – 23 (2019).

94 Article 2, *Ibid*.

95 Article 3(2)(b), *Ibid*.

96 Article 2, *Ibid*.

97 Article 5 and following , *Ibid*.

98 Articles 5 and following, Regulation (EU) 2019/6 and Article 13, Regulation (EU) 2019/4.

99 Articles 5 and following, Regulation (EU) 2019/6 and Article 14, Regulation (EU) 2019/4.

100 Annex III, Regulation (EU) 2019/4 and Article 10(2), Regulation (EU) 2019/6.

101 *Ibid*, Regulation (EU) 2019/4.

102 Article 119 and 120, Regulation (EU) 2019/6 and Article 11, Regulation (EU) 2019/4.

103 Article 119 (9), Regulation (EU) 2019/6 and Article 11, Regulation (EU) 2019/4.

104 Article 106, *Ibid*.

105 Article 110, *Ibid*.

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106 Article 105(2) et (3)

107 Article 105(1)

108 Article 107(1)

109 Article 107(1)

110 Article 107(2)

111 Article 107(2)

112 Article 107(3)

113 *Ibid*.

114 Article 107(4)

115 Article 107 (5). Such a list will be enacted by way of an implementing act.

- **Prescription and Examination Requirements**

The use of antimicrobials in animals for both metaphylaxis and prophylaxis purposes is allowed only if such a treatment has been prescribed by a veterinarian. The prescribing veterinarian must be able to justify usage, after having conducted a "clinical examination or any other proper assessment of the health status of the animal or group of animals."[106] By definition, in the case of antimicrobials used for metaphylaxis purposes, the veterinarian must further provide a diagnosis.[107]

- **Prohibition on uses**

Furthermore, certain uses of antimicrobials are prohibited, as follows:

Table 1 : Prohibited uses of antimicrobials

	PROHIBITED USES	EXEMPTION
Use related to the administration frequency	Routine use.[108]	None, but the term "routinely" is not defined.
Use related to the purpose	Use for the purpose of compensating for poor hygiene, inadequate animal husbandry, lack of care, or poor farm management.[109]	None, but what constitutes "poor hygiene, inadequate animal husbandry, lack of care, or poor farm management" is not defined.
	Use for the purpose of promoting growth.[110]	None
	Use for the purpose of increasing yield.[111]	None
	Use for prophylactic purposes.[112]	1. For an individual animal. 2. Or a "restricted number of animals when the risk of an infection or of an infectious disease is very high and the consequences are likely to be severe."[113] 3. Or in a group "when the risk of spread of an infection of an infectious disease is very high and where no other appropriate alternatives are available."[114]
Use of certain substances	The use of antimicrobials reserved for treatment of certain infections in humans.[115]	None

Under the **Medicated Feed Regulation,** the use of medicated feed is subject to the following cumulative conditions:

The presentation of a veterinary prescription; [116]

Delivered by a veterinarian;[117]

Who has examined the animal or the group of animals;[118]

And who has diagnosed a disease in this or these animals.[119]

However, certain exemptions apply: *(see Table 3)*

Under both regulations, the veterinary prescription must further comply with a set of specifications, including the full name and contact information of the veterinarian, the issue and expiration dates of the prescription, the full name of the animal keeper, the designation of the veterinary medicinal product, and the quantity of medicated feed.[123] The validity of a veterinary prescription for medicated feed for animals used for food and fur purposes is limited to three weeks from the date of issuance.[124] Finally, the original and copies of the prescription must be kept for five years from the date of issuance.

- *Record Keeping Requirements*

• Sales by retailers

The Veterinary Medicinal Product regulation provides that retailers of veterinary medicinal products must keep "detailed records of the [...] information in respect of each transaction of veterinary medicinal products requiring a veterinary prescription."[125]

- *Use by keepers*

Furthermore, owners and keepers of food-producing animals must keep records of the veterinary medicinal products as well as the medicated feed they use and, where applicable, a copy of the veterinary prescription.[126] Such records must include the name and quantity of the product administered and the identification of the animal(s) treated.[127]

- *Equivalence Rules for Imports*

Producers of animals or animal source-products from outside the EU must comply with the prohibition on the use of antimicrobials used for the purpose of promoting growth and to increase yield.[128]

- *Disposal*

Both regulations require that Member States implement a system for the collection or discard on unused or expired intermediate products and medicated feed.[129]

- *Enforcement*

Finally, Member States must adopt "effective, proportionate, and dissuasive" penalties in cases of breaches with the regulation, by the date of entry into force of the act (January 28th 2022).[130]

Table 3 : Requirements for the use of medicated feed

RULE	EXEMPTION
1. Presentation of a veterinary **prescription**;	None
2. Delivered by a **veterinarian**;	Member States may allow non-veterinarian professionals to issue prescriptions for medicated feed. However, the prescription of medicated feed containing antimicrobials must always be prescribed by a veterinarian.[120]
3. Who has examined the animal or the group of **animals**;	For medicated feed containing antiparasitics without antimicrobial effects, the knowledge of the parasite infection in the animal(s) is enough to issue a prescription.[121]
4. And who has **diagnosed a disease** in this or these animals.	The presence of a diagnosed disease is not required for the prescription of feed containing immunological veterinary medicine products.[122]

116 Article 16 (1)(a), Regulation (EU) 2019/6.

117 Article 16 (2), *Ibid*.

118 *Ibid*.

119 *Ibid*.

120 Article 16 (5), *Ibid*.

121 Article 16 (4), *Ibid*.

122 Article 16 (3), *Ibid*.

123 Article 16 (6), Annex V, *Ibid*.

124 Article 16 (8), *Ibid*.

125 Article 103, Regulation (EU) 2019/6.

126 Article 17(7), Regulation (EU) 2019/4 and Article 108, Regulation (EU) 2019/6.

127 Article 108, *Ibid*.

128 Article 118, Regulation (EU) 2019/6.

129 Article 117, Regulation (EU) 2019/6 and Article 18, Regulation (EU) 2019/4.

130 Article 135, Regulation (EU) 2019/6 and Article 22, Regulation (EU) 2019/4.

3.2.2. EXAMPLES OF GOOD IMPLEMENTATION PRACTICES AT NATIONAL LEVEL

- Antibiotics Classification in France

  Article L 5144-1-1- Code de la Santé publique[131] prohibits the use of critically important antibiotic substances for use in veterinary medicine, with the exception of second-generation quinolones (fluoroquinolones), for the use in ophthalmology of companion animals and equines for topical administration. Drugs containing one or more antibiotic substances of critical importance listed are prohibited in veterinary medicine for preventive use. Furthermore, critically important antimicrobials can be used for curative and metaphylaxic use as long as laboratory results indicate that the bacterial strain identified is sensitive only to this critical antibiotic substance.

- Surveillance in Use in Italy and Spain

  Italian[132] and Spanish[133] law both require the use of e-prescriptions for veterinary medicines and medicated feed containing antimicrobials. This ensures data collection of antimicrobials used in animal agriculture.

3.3. Limitations

The Veterinary Medicinal Products Regulation prohibits the routine use of antimicrobials and the use of antimicrobials to "compensate for poor hygiene, inadequate animal husbandry, lack of care, or poor farm management."[134] However, the legislation never provides specifications as to what would constitute a routine use of antimicrobials, by setting, for instance, a frequency of use above which the use is considered to be routine. Similarly, what is "poor hygiene, inadequate animal husbandry, lack of care, or poor farm management" is not substantiated by quantifiable standards, and thus remains to be a subjective assessment conducted by business operators.

A second important limitation is the difficulty to draw the line between prophylactic use, which is allowed under the Veterinary Medicinal Products Regulation, and the use for growth promotion, which is not.
Yet, given that the risk of infection is inherent to animal agriculture, farmers can potentially always justify subtherapeutic use by arguing that they are administering antibiotics for preventive purposes.

Finally, the criteria for antimicrobials reserved for the treatment of certain infections in humans was established in Commission Delegated Regulation 2021/1760[135]. Per this regulation, an antimicrobial is deemed reserved for humans if it meets the following three criteria:

- It is of high importance to human health
- It poses a risk of transmission of antimicrobial resistance
- It is not essential for animal health

This list adds a third criterion which is in addition to the two established by the WHO; the third criterion here is the non-essential need for animal health. This deviation from the WHO criteria has the effect of setting the bar particularly high for the designation of antimicrobials reserved for humans, while prioritizing animal health over human and environmental health.[136]

131 L 5144-1-1- Code de la santé publique and R 5141 - 117 - 3 Code de la santé publique, 2016 (Fr.). *See also* The Coller Foundation, "The Coller Animal Law Forum," https://calf.law/ (last visited December 11th 2021).

132 Decreto 8 febbraio 2019 Modalità applicative delle disposizioni in materia di tracciabilità dei medicinali veterinari e dei mangimi medicati (It.). *See also* The Coller Foundation, "The Coller Animal Law Forum," https://calf.law/ (last visited December 11th 2021).

133 Real Decreto 191/2018, de 6 de abril, por el que se establece la transmisión electrónica de datos de las prescripciones veterinarias de antibióticos destinados a animales productores de alimentos para consumo humano (Spain). *See also* The Coller Foundation, "The Coller Animal Law Forum," https://calf.law/ (last visited December 11th 2021).

134 Article 107(1), Regulation (EU) 2019/6.

135 Commission Delegated Regulation (EU) 2021/1760 of 26 May 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by establishing the criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans, O.J. L 353/ 1–5 (2021).

136 European Parliament, Motion for a Resolution on the Commission delegated regulation of 26 May 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by establishing the criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans, Committee on the Environment, Public Health, and Food Safety, July 6th 2021, available online: https://www.europarl.europa.eu/meetdocs/2014_2019/plmrep/COMMITTEES/ENVI/DV/2021/07-12/RE_Objection_DA_antimicrobials_2021_EN.pdf.

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Alice Di Concetto, LL.M
European Institute for Animal Law & Policy
alice@animallaweurope.com

Grace Martin, MChem, MSc
Intern at FAIRR, February - October 2021

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· EU law

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Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC, O.J. L 4/1 – 23 (2019)

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/ 43–167 (2019)

· National Legislation

L 5144-1-1- Code de la santé publique and R 5141 - 117 - 3 Code de la santé publique, 2016 (Fr.)

Real Decreto 191/2018, de 6 de abril, por el que se establece la transmisión electrónica de datos de las prescripciones veterinarias de antibióticos destinados a animales productores de alimentos para consumo humano (Spain)

Decreto 8 febbraio 2019, Modalità applicative delle disposizioni in materia di tracciabilità dei medicinali veterinari e dei mangimi medicati (It.).

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Annex 1

137 World Health Organization, Critically Important Antimicrobials for Human Medicine, 6th Edition (2018), available online at: https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf.

138 *Ibid*.

139 *Ibid*.

140 *Ibid*.

141 Compassion in World Farming, Antibiotics in Animal Farming: Public Health and Animal Welfare (2011), available online: https://www.ciwf.org.uk/media/3758863/Antibiotics-in-Animal-Farming-Public-Health-and-Animal-Welfare.pdf

142 American Veterinary Medical Association, "Judicious Therapeutic Use of Antimicrobials," http://www.avma.org/issues/policy/jtua.asp (last visited December 11th 2021).

LEXICON

Antibiotics: Any substance that destroys or inhibits the growth or replication of bacteria or certain fungi. Antibiotics are a type of antimicrobial which are primarily used in the prevention and treatment of infectious bacterial diseases. They are not effective in treating infections caused by viruses.

Antimicrobial residues: Trace amounts in any edible portion of the animal product after the administration of antimicrobials in an animal or an animal-source product.

Antibiotic Resistance: Antibiotic resistance is a subset of AMR (see antimicrobial resistance), which occurs when bacteria evolve over time and consequently no longer respond to formerly effective antibiotics.

Antimicrobial Resistance (AMR): A phenomenon whereby microorganisms (bacteria, fungi, parasites, and viruses) become partially or fully resistant to antimicrobial drugs that they were once susceptible to. Antimicrobials include antibiotics, antifungal, antiprotozoal and antivirals. These resistant microorganisms consequently no longer respond to medicines, making infections increasingly difficult and in some cases impossible to treat. Antimicrobial resistance is a natural phenomenon but is accelerated by the overuse and misuse of antimicrobials.

Antimicrobials: Drugs that destroy or inhibit the growth of microorganisms (for instance bacteria, viruses, fungi, and parasites). Antimicrobial drugs are used to treat microbial infections caused by pathogens. An antibiotic drug is an antimicrobial. However, not all antimicrobials are antibiotics.

Critically important antimicrobials (CIAs): CIAs are antimicrobials deemed by the WHO as critically important to human medicine[137] because they meet the following two criteria: the sole therapy (or one of limited available therapies) to treat serious bacterial infections in people, and a therapy used to treat infection caused by bacteria where there is a potential path for acquisition of resistance, either now or in the future[138]. CIAs are sub-divided into "High Priority" and "Highest Priority Critically Important Antibiotics. [139]

Ionophores: Ionophores are a class of antimicrobial widely used in industrial farm animal production. They are used as coccidiostats in poultry farming to treat coccidiosis and are fed to cattle to improve production efficiency. Their classification differs across jurisdictions. Ionophores are classified as antibiotics in the US but not in the UK, where they are classified as feed additives. At present, ionophores are too toxic to be used in human medicine and so are not currently considered to be medically important. There is debate over whether the overuse of ionophores leads to increased antibiotic resistant mechanisms in humans.

Judicious Use of Antimicrobials: As opposed to routine use of antimicrobials,, judicious use of antimicrobials consists in the restriction of antimicrobial use, including by prohibiting their use for growth promotion purposes and to compensate for poor welfare levels and unsanitary conditions on farms.

Medically important antimicrobials (MIAs): MIAs refer to the list of antimicrobials the WHO has designated as important to human medicine. This term encompasses antibiotics defined as "critically important," "highly important" and "important" to human medicine. [140]

143 Article 4(16), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/57 (2019).

144 Compassion in World Farming, Antibiotics in Animal Farming: Public Health and Animal Welfare (2011), available online: https://www.ciwf.org.uk/media/3758863/Antibiotics-in-Animal-Farming-Public-Health-and-Animal-Welfare.pdf

145 *Ibid.*

146 *Ibid.*

147 Article 4(34), Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, O.J. L 4/ 58 (2019).

Metaphylaxis: A type of therapeutic use that corresponds to the use of a high dose of antibiotics to treat a whole herd or flock when a few animals are found to be carrying an infectious disease to prevent the disease from spreading. However, the distinction between treatment and prevention is often unclear.[141][142]

Prophylaxis: Also referred to as "prophylactic use," prophylaxis is a type of non-therapeutic use that corresponds to the administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection.[143] Prophylaxis use can be routine and is usually administered at low dosage through drinking water or feed.[144]

Superbugs: An informal term that refers to strains of bacteria, viruses, parasites, and fungi that have formed resistance to multiple antibiotics and other commonly used medications.

Therapeutic use: The use of antibiotics to treat disease that has been diagnosed by a licensed veterinarian. This term refers to the treatment of specific illness, as opposed to non-therapeutic or prophylactic use (*see* **non-therapeutic use** *or* **prophylaxis**). The treatment dose is typically very high and occurs for a short period of time.[145]

Non-therapeutic use: The non-therapeutic use of antibiotics involves the administration of low, subtherapeutic doses of antimicrobial agents to healthy animals to control the spread of infections (which would otherwise proliferate under intensive farming methods) (*see* **prophylaxis**) or to stimulate unnatural growth and productivity.[146] These are typically administered through the feed or water. Many of the antimicrobial agents used for non-therapeutic uses are the same as those used to cure disease, including in humans.

Routine use of antimicrobials: The liberal use of antimicrobials as opposed to antimicrobial stewardship, an approach that advocates for a **judicious use of antimicrobials.**

Withdrawal period: The minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health.[147]

RESISTING ANTIMICROBIAL RESISTANCE [...] RESEARCH NOTE #4

Annex 2

LIST OF GLOBAL AND EU ADMINISTRATIONS AND AGENCIES

GLOBAL AGENCIES

148 Article 2, Constitution of the World Health Organization, United Nations, 1946.

149 Article 4, Organic Statutes of the Office International des Epizooties, 1924.

WORLD HEALTH ORGANIZATION

Year of creation: 1948

Headquarters: Geneva, Switzerland

Director: Tedros Adhanom

Mandate: Among many missions, the WHO "acts as the directing and coordinating authority on international health work"[148]

Key policies on antimicrobial resistance:

WORLD ANIMAL HEALTH ORGANIZATION (OIE)

Year of creation: 1924 (formerly: "Office International des Epizooties")

Headquarters: Paris, France

Director: Monique Eloit

Mandate: Promoting and coordinating "all experimental and other research work concerning the pathology or prophylaxis of contagious diseases of livestock for which international collaboration is deemed desirable."[149]

Key policies on antimicrobial resistance: The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials (2016).

UNITED NATIONS' FOOD AND AGRICULTURE ORGANIZATION (FAO)

Year of creation: 1945

Headquarters: Rome, Italy

Director: Qu Dongyu

Mandate: As a special agency of the UN, the FAO leads international efforts to defeat hunger by improving nutrition, increasing agricultural productivity and sustainability, and improving the lives of rural communities. The FAO also sets standards to harmonize food production in the world through its Codex Alimentarius.

Key policies on antimicrobial resistance: The FAO Action Plan on Antimicrobial Resistance 2021–2025 (2021); Antimicrobial Resistance and the United Nations Sustainable Development Cooperation Framework: Guidance for United Nations Country Teams (2020) (with the OIE, WHO, and UNEP); Responsible Use of Antimicrobials in Beekeeping (2016).

EU ADMINISTRATIONS AND AGENCIES

DIRECTORATE GENERAL FOR PUBLIC HEALTH AND FOOD SAFETY (DG SANTE)

Year of creation: 1999

Headquarters: Brussels, Belgium

Director: Stella Kyriakides

Mandate: Carries out develops and carries out the Commission's policies on food safety and public health. Its mandate is limited to coordinating EU Member States given that public health is not an EU competence, that the EU only has shared competence when it comes to "common safety concerns in public health matters."[150]

Key policies on antimicrobial resistance: European Commission, A European One Health Action Plan Against Antimicrobial Resistance (AMR) (2017).

150 Article 3, Treaty on European Union, O.J. C 326/ 17 (2012) ; Article 4(2)k) Treaty on the Functioning of the European Union, Consolidated version of the Treaty on the Functioning of the European Union, O.J. C 326/51 (2012).

EUROPEAN CENTER FOR DISEASE PREVENTION AND CONTROL (ECDC)

Year of creation: 2005)

Headquarters: Stockholm, Sweden

Director: Andrea Ammon

Mandate: "Identify, assess and communicate current and emerging threats to human health from communicable diseases."[151]

Key policies on antimicrobial resistance: Alessandro Cassini et al., Attributable Deaths and Disability-Adjusted Life-Years Caused by Infections with Antibiotic-Resistant Bacteria in the EU and the European Economic Area in 2015: a Population-Level Modelling Analysis, The Lancet Infectious disease (2019).

151 Article 3(1), Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 april 2004 establishing a European Centre for disease prevention and control, O.J. L 142/ 1–11 (2004).

EUROPEAN ENVIRONMENTAL AGENCY

Year of creation: 1993

Headquarters: Copenhagen, Denmark

Director: Hans Bruyninckx

Mandate: Among other mission, the EEA is tasked with "providing the Community and the Member States with the objective information necessary for framing and implementing sound and effective environmental policies"[152]

152 Article 2(b), Regulation (EC) No 401/2009 of the European Parliament and of the Council of 23 April 2009 on the European Environment Agency and the European Environment Information and Observation Network, O.J. L 126/ 14 (2009).

EU ADMINISTRATIONS AND AGENCIES

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

Year of creation: 2002

Headquarters: Parma, Italy

Director: Bernhard Url

Mandate: Provide independent information and "scientific advice, as well as scientific and technical support for the Community's legislation and policies in all fields which have a direct or indirect impact on food and feed safety."[153]

Key policies on antimicrobial resistance: All the EFSA opinion on the safety on the use of antimicrobial substances.[154]

153 Article 22(2), Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, O.J. L 31/ 1 - 24 (2002).

154 Available online: https://www.efsa.europa.eu/en/publications (last visited December 12th, 2021).

EUROPEAN MEDICINES AGENCY (EMA)

Year of creation: 2015

Headquarters: Amsterdam, the Netherlands

Director: Emer Cooke

Mandate: Coordinating "the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products." EMA is also responsible for assessing maximum residue limits for veterinary medicinal product[155]s marketed in the EU.

Key policies on antimicrobial resistance: Creation of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) in 2009, which collects information on how antimicrobial medicines are used in animals across the EU.

155 Article 55, Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, O.J. L 136/22 (2004).

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