Regulatory Strategies To Combat Antimicrobial Resistance of Animal Origin: Recommendations for a Science-Based U.S. Approach

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Debate over how regulation can address the growing public health crisis of antimicrobial resistance has addressed both the regulatory framework for intervention and the political choice to intervene, balancing control of the public health risk from agricultural use of antimicrobials and economic benefit to agribusiness from such use. This Article presents an update on the scientific evidence to support a need to regulate, with a review of current U.S. laws and regulations pertaining to nontherapeutic use of antimicrobials in livestock and to surveillance of antimicrobial-resistant pathogens of food animal origin. Regulatory efforts in the United States and Europe are compared, with an emphasis on the scientific evidence for public health success or failure of these policy interventions. The Article concludes with a discussion of how the science of antimicrobial resistance can inform regulatory efforts in U.S. and global efforts to address the problem. Recommendations for combined regulatory, surveillance, and research strategies are offered, with a focus on science-based regulatory approaches and mechanisms for evaluation of the public health benefits of regulation.

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I. INTRODUCTION

For World Health Day 2011, the World Health Organization (WHO) called for governments and drug regulatory agencies to coordinate a

response to the urgent problem of antibiotic drug resistance.[1] To do this, strong, multifaceted regulatory efforts both at the domestic and international levels are needed. Antimicrobial drugs, including antibiotics,[2] are important to human and veterinary medicine for the treatment of infectious diseases.[3] However, bacteria may develop resistance to one or more classes of antibiotics, allowing them to survive and reproduce even in the presence of these drugs.[4] When antibiotic-resistant pathogens cause infection, the human and economic costs are high.[5] In the United States, human health care costs associated with treating diseases resistant to antibiotics are estimated at over four billion dollars annually[6] and may reach seven billion dollars.[7] Patients infected with resistant bacteria generally have higher mortality, higher morbidity, longer hospital stays, and higher rates of sequelae than those with susceptible infections.[8]

Bacteria can acquire genes for resistance from other bacteria, and this process of genetic exchange can occur in microorganisms carried by humans and animals, or present in the environment.[9] Because of this

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1. *World Health Day 2011: Director-General Statement*, WORLD HEALTH ORG. (2011), http://www.who.int/world-health-day/2011/presskit/WHD2011-DGstate-EN.pdf.

2. In this Article, the terms "antimicrobial" and "antibiotic" may occasionally appear to be used interchangeably, because antibiotics are, by some definitions, considered to be antimicrobials. Not all antimicrobials are antibiotics, however. Some regulations may apply to all antimicrobials broadly (used to treat infections with viruses, bacteria, parasites, and fungal organisms), and others to drugs used to treat bacterial infections specifically. Technically, the term "antibiotic" refers only to chemicals naturally produced by microorganisms that kill or impair other microorganisms; otherwise, synthetic antibiotics are considered antimicrobials. For a lay definition of these terms, see Luca Guardabassi & Patrice Courvalin, *Modes of Antimicrobial Action and Mechanisms of Bacterial Resistance*, *in* ANTIMICROBIAL RESISTANCE IN BACTERIA OF ANIMAL ORIGIN 1, 1 (Frank M. Aarestrup ed., 2006) (concerning use and misuse of the terms antimicrobial and antibiotic) and *Antibiotic/Antimicrobial Resistance*, CENTERS FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/drugresistance/index.html (last visited Mar. 20, 2012).

3. Peter Lees et al., *Drug Selection and Optimization of Dosage Schedules To Minimize Antimicrobial Resistance*, *in* ANTIMICROBIAL RESISTANCE IN BACTERIA OF ANIMAL ORIGIN, *supra* note 2, at 49.

4. *Id.* at 50.

5. AM. SOC'Y FOR MICROBIOLOGY, REPORT OF THE ASM TASK FORCE ON ANTIBIOTIC RESISTANCE 7-8 (1995), http://www.asm.org/images/docfilename/0000005962/antibiot[1].pdf; Oguz Resat Sipahi, *Economics of Antibiotic Resistance*, 6 EXPERT REV. ANTI-INFECTIVE THERAPY 523, 526 (2008).

6. AM. SOC'Y FOR MICROBIOLOGY, *supra* note 5, at 3.

7. Joanna Coast & Richard D. Smith, *Antimicrobial Resistance: Cost and Containment*, 1 EXPERT REV. ANTI-INFECTIVE THERAPY 241, 242 (2003) (citing Joseph F. John, Jr. & Neil O. Fishman, *Programmatic Role of the Infectious Diseases Physician in Controlling Antimicrobial Costs in the Hospital*, 24 CLINICAL INFECTIOUS DISEASES 471 (1997)).

8. Sipahi, *supra* note 5, at 526.

9. John F. Prescott, *History of Antimicrobial Usage in Agriculture: An Overview*, *in* ANTIMICROBIAL RESISTANCE IN BACTERIA OF ANIMAL ORIGIN, *supra* note 2, at 19, 26 fig.1

complex ecology, use of antibiotics in one setting, such as agriculture, can drive emergence of resistant bacteria capable of causing disease in humans.[10] In food-producing animals,[11] antimicrobials either may be administered to treat disease or used at low levels in feed to promote animal growth, which the industry claims improves feed efficiency and controls intestinal pathogens.[12] However, this latter use of antimicrobial drugs (for growth promotion)[13] typically involves feeding them to animals at levels that result in doses that are not high enough to kill or inhibit all target bacteria[14] (i.e., at concentrations below those required to treat clinical infection).[15] This drives emergence of resistant organisms in those animals and in the environment.[16] Use of antimicrobial drugs in agriculture exceeds that in human clinical settings nearly eight-fold.[17] In

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(adapted from A.H. Linton, *Antibiotic Resistance: The Present Situation Reviewed*, 100 VETERINARY REC. 354 (1977) and modified by R. Irwin from a model sometimes referred to as the "confusogram").

10. Ellen K. Silbergeld et al., *Industrial Food Animal Production, Antimicrobial Resistance, and Human Health*, 29 ANN. REV. PUB. HEALTH 151, 153 (2008); Mary J. Gilchrist et al., *The Potential Role of Concentrated Animal Feeding Operations in Infectious Disease Epidemics and Antibiotic Resistance*, 115 ENVTL. HEALTH PERSP. 313, 313-14 (2007); F.J. Angulo et al., *Antimicrobial Resistance in Zoonotic Enteric Pathogens*, 23 SCI. & TECHNICAL REV. 485, 485-86 (2004); Scott A. McEwen & Paula J. Fedorka-Cray, *Antimicrobial Use and Resistance in Animals*, 34 CLINICAL INFECTIOUS DISEASES S93, S99-100 (Supp. 2002).

11. Food-producing animals, also known as livestock or food animals, include all animals raised for meat, milk, or eggs for human consumption. Pigs, poultry ("layer" chickens which produce eggs, "broiler" chickens raised for meat, and turkeys), dairy cows, beef cattle, and farmed fish (e.g., catfish) are examples of the most common food-producing animals raised in the United States. *See generally* 1 U.S. DEP'T OF AGRIC. (USDA), 2007 CENSUS OF AGRICULTURE (2009), http://www.agcensus.usda.gov/Publications/2007/Full_Report/usv1.pdf.

12. *See* Prescott, *supra* note 9, at 22.

13. The practice of feeding antimicrobials at levels below that which treat clinical infection, alternately termed "nontherapeutic" or "subtherapeutic" use, originated in the late 1940s and early 1950s. During that era, this use was shown to hasten animal weight gain and, at times, reduce mortality in herds or flocks. In the United States, "subtherapeutic levels" sometimes are defined as concentrations of antimicrobials that are less than two hundred grams per ton of feed. The degree to which this use remains an economic incentive for an individual farmer or industrial producer depends on many factors, including the underlying health and environmental living conditions of the animals. *See id.* at 19-22.

14. Antimicrobial drugs differ in their ability to kill (*bacteriocidal* drugs) or inhibit (*bacteriostatic* drugs) different kinds of bacteria. For example, fluoroquinolone drugs (e.g., ciprofloxacin and enrofloxacin) are broad-spectrum and are active against gram-negative bacteria (e.g., *E. coli*) and gram-positive cocci (e.g., *Staphylococcus aureus*), but have only weak activity against anaerobic bacteria (e.g., *Clostridium*). *See id.* at 22-23.

15. *Id.*

16. Silbergeld et al., *supra* note 10, at 151-53, 162-63; Gilchrist et al., *supra* note 10, at 313-14; Frederick J. Angulo et al., *Antimicrobial Use in Agriculture: Controlling the Transfer of Antimicrobial Resistance to Humans*, 15 SEMINARS PEDIATRIC INFECTIOUS DISEASES 78, 78-79 (2004).

17. MARGARET MELLON ET AL., HOGGING IT!: ESTIMATES OF ANTIMICROBIAL ABUSE IN LIVESTOCK, at xiii (2001).

2010, the Food and Drug Administration (FDA) reported that 13.2 million kilograms (over twenty-nine million pounds) of antimicrobials were sold or distributed domestically for use in food-producing animals.[18] Agricultural uses represented 80% of the antimicrobial drug sales in the United States, and over 90% of these antimicrobials were administered in animal feed or water.[19]

The regulation of antimicrobial use in agriculture has received attention at the national and global levels in recent years. In 1997, the WHO held the first of many conferences on antimicrobial resistance,[20] and designated certain antimicrobials "critically important"[21] to human health during a later conference in Canberra.[22] In 1998, the European Union (EU) passed a commission ruling banning the use of a number of antimicrobials in animal feed.[23] A study of the impact of the ban in Denmark showed little economic impact to that country's broiler chicken industry, although the swine industry experienced a 1% increase in overall costs of production.[24] Offsetting this minor cost was a tremendous decrease in the percentage of bacteria from swine and broiler

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18. This estimate includes all uses in food-producing animals for all purposes (growth promotion, prophylaxis, or therapy), and regardless of route of administration (via injection, oral administration, or in medicated feed). *See* CTR. FOR VETERINARY MED., FDA, 2010 SUMMARY REPORT ON ANTIMICROBIALS SOLD OR DISTRIBUTED FOR USE IN FOOD-PRODUCING ANIMALS, at iii, iv tbl.1 (2011), http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM277657.pdf.

19. Letter from Karen Meister, Supervisory Cong. Affairs Specialist, FDA, to Representative Louise M. Slaughter, U.S. House of Representatives (Apr. 19, 2011), http://www.louise.house.gov/images/stories/FDA_Response_to_Rep._Slaughter.pdf; MELLON ET AL., *supra* note 17, at xiii.

20. *See* WORLD HEALTH ORG. [WHO], THE MEDICAL IMPACT OF ANTIMICROBIAL USE IN FOOD ANIMALS (1997), http://whqlibdoc.who.int/hq/1997/WHO_EMC_ZOO_97.4.pdf (outlining the medical impact of antimicrobial use in food animals that was discussed at a WHO meeting in Berlin, Germany, in October 1997).

21. *See* WHO, CRITICALLY IMPORTANT ANTIBACTERIAL AGENTS FOR HUMAN MEDICINE FOR RISK MANAGEMENT STRATEGIES OF NON-HUMAN USE 4-5 (2005), http://www.who.int/foodborne_disease/resistance/amr_feb2005.pdf. Two criteria were used by WHO to determine the importance of antibiotics that may be used in food-producing animal production for human health. The first criterion was the importance of the drug in human health, i.e., whether or not the drug was the only or one of few available to treat a given disease. The second criterion was the use of a given antibiotic to treat specifically zoonotic disease, i.e., a disease that can be transmitted from an animal to a human. These were given a higher weight. *Id.*

22. *Id.*

23. *See* Frank Møller Aarestrup et al., *Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark*, 45 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 2054, 2054 (2001).

24. Hanne-Dorthe Emborg & Henrik C. Wegener, *The Effect of Banning Antibiotics for Growth Promotion in Poultry and Swine Production in Denmark*, *in* 2 PERSPECTIVES IN WORLD FOOD AND AGRICULTURE 161, 168-69 (John A. Miranowski & Colin G. Scanes eds., 2005) (citing WHO, IMPACTS OF ANTIMICROBIAL GROWTH PROMOTER TERMINATION IN DENMARK (2003)).

chickens that were resistant to the banned antimicrobials.[25] This suggests that regulation may offer an effective public health strategy to combat antimicrobial resistance of agricultural origin.

Scientists,[26] professional organizations,[27] public health advocates,[28] and the U.S. General Accounting Office[29] have argued that the U.S. government's current oversight of antimicrobial use in agriculture is insufficient to address the problem of rising antimicrobial resistance. Within the last forty years, the FDA has developed primarily nonbinding guidance about the use of nontherapeutic antimicrobials in livestock in the United States.[30] Congressional efforts to give legal effect to the principles of appropriate antimicrobial use described in this guidance have failed, and the FDA's guidance continues to lack enforceability.[31] Agribusiness has opposed legislation requiring reduction or elimination of nontherapeutic use of antimicrobials in livestock.[32]

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25. *Id.* at 163-67.

26. Silbergeld et al., *supra* note 10; Gilchrist et al., *supra* note 10; McEwen & Fedorka-Cray, *supra* note 10.

27. AM. SOC'Y FOR MICROBIOLOGY, *supra* note 5; John G. Bartlett et al., *Statement of the Infectious Diseases Society of America Before the Food and Drug Administration Part 15 Hearing Panel on Antimicrobial Resistance*, INFECTIOUS DISEASES SOC'Y AM. (Apr. 28, 2008), http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Antimicrobials/Statements/ee434daf62ba4fedac689288741635704.pdf.

28. PEW COMM'N ON INDUS. FARM ANIMAL PROD., PUTTING MEAT ON THE TABLE: INDUSTRIAL FARM ANIMAL PRODUCTION IN AMERICA (2008), http://www.ncifap.org/_images/PCIFAPFin.pdf; MELLON ET AL., *supra* note 17, at xi-xiv.

29. *See* U.S. GEN. ACCOUNTING OFFICE, GAO-04-490, ANTIBIOTIC RESISTANCE: FEDERAL AGENCIES NEED TO BETTER FOCUS EFFORTS TO ADDRESS RISK TO HUMANS FROM ANTIBIOTIC USE IN ANIMALS (Apr. 2004), http://www.gao.gov/assets/250/242186.pdf.

30. *E.g.*, CTR. FOR VETERINARY MED., FDA, GUIDANCE FOR INDUSTRY: EVALUATING THE SAFETY OF ANTIMICROBIAL NEW ANIMAL DRUGS WITH REGARD TO THEIR MICROBIOLOGICAL EFFECTS ON BACTERIA OF HUMAN HEALTH CONCERN (Oct. 23, 2003), http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf.

31. Donald Kennedy, Op-Ed, *Cows on Drugs*, N.Y. TIMES, Apr. 18, 2010, at WK11; *Preservation of Antibiotics for Medical Treatment Act (PAMTA): Hearing on H.R. 1549 Before the H. Comm. on Rules*, 111th Cong. 7 (2009) (statement of Joshua M. Sharfstein, Principal Deputy Comm'r of Food and Drugs, FDA).

32. *See* Kennedy, *supra* note 31; *Political Bans on Antibiotics Are Counterproductive—European Test Case: Increased Animal Disease, Mixed Human Health Benefit*, AM. FARMERS FOR ADVANCEMENT & CONSERVATION TECH., http://www.itisafact.org/media/factsheets/danish%20experience.pdf (last visited Mar. 21, 2012); AM. VETERINARY MED. ASS'N, S. 619/H.R. 1549—PRESERVATION OF ANTIBIOTICS FOR MEDICAL TREATMENT ACT OF 2009, http://www.avma.org/advocacy/federal/legislative/111th/issue_briefs/Preservation_of_Antibiotics_Act_of_2009_Issue_Brief.pdf (last visited Mar. 21, 2012); *see also* Eric Gonder, Letter to the Editor, *Poultry Veterinarians' Perspectives on Antimicrobial Resistance*, 237 J. AM. VETERINARY MED. ASS'N 258 (2010); Becky Tilley, Letter to the Editor, *Poultry Veterinarians' Perspectives on Antimicrobial Resistance*, 237 J. AM. VETERINARY MED. ASS'N 258, 258-59 (2010).

Regulatory strategies to address antimicrobial resistance, particularly of food animal origin, have been considered extensively in recent legal literature.[33] As Terence Centner's article about regulating nontherapeutic use of antimicrobials in food-producing animals explains, "Scientists and policy makers must continue to learn more about the complex epidemiology of resistant pathogens and the risks accompanying bans of non-therapeutic antibiotics."[34] In a 2009 article, Halpern commented, "While scientific knowledge has expanded, significant gaps remain in our understanding of the physiologic and epidemiologic nature of antibiotic resistance . . . . These uncertainties present a serious challenge to policy-makers attempting to base important decisions on sound science."[35] While these articles and others provide perspectives on how (in a legal sense) to regulate antimicrobials, none addresses how (in a scientific sense) regulatory strategies may more effectively address the scientific problem of antimicrobial resistance. This Article will argue that current scientific evidence is sufficient to support regulatory efforts regarding the use of antimicrobials in agriculture, accounting for the inherent uncertainties common to all research noted by Halpern. A science-based approach to regulation emphasizes an obligation to not only apply public dollars for evidence-based strategies to improve the public's health, but also to evaluate the

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33. Vanessa K.S. Briceño, *Superbug Me: The FDA's Role in the Fight Against Antibiotic Resistance*, 9 N.Y.U. J. LEGIS. & PUB. POL'Y 521 (2005); Terence J. Centner, *Regulating the Use of Non-Therapeutic Antibiotics in Food Animals*, 21 GEO. INT'L ENVTL. L. REV. 1 (2008); Robyn L. Goforth & Carol R. Goforth, *Appropriate Regulation of Antibiotics in Livestock Feed*, 28 B.C. ENVTL. AFF. L. REV. 39 (2000); Nancy E. Halpern, *Antibiotics in Food Animals: The Convergence of Animal and Public Health, Science, Policy, Politics and the Law*, 14 DRAKE J. AGRIC. L. 401 (2009); Eric Kades, *Preserving a Precious Resource: Rationalizing the Use of Antibiotics*, 99 NW. U. L. REV. 611 (2005); Barbara O'Brien, *Animal Welfare Reform and the Magic Bullet: The Use and Abuse of Subtherapeutic Doses of Antibiotics in Livestock*, 67 U. COLO. L. REV. 407 (1996); William M. Sage & David A. Hyman, *Combating Antimicrobial Resistance: Regulatory Strategies and Institutional Capacity*, 84 TUL. L. REV. 781 (2010); Scott B. Markow, Note, *Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse*, 87 GEO. L.J. 531 (1998); Michael Misocky, Comment, *The Epidemic of Antibiotic Resistance: A Legal Remedy To Eradicate the "Bugs" in the Treatment of Infectious Diseases*, 30 AKRON L. REV. 733 (1996); Anastasia S. Stathopoulos, Note, *You Are What Your Food Eats: How Regulation of Factory Farm Conditions Could Improve Human Health and Animal Welfare Alike*, 13 N.Y.U. J. LEGIS. & PUB. POL'Y 407 (2010); Graham M. Wilson, Note, *A Day on the Fish Farm: FDA and the Regulation of Aquaculture*, 23 VA. ENVTL. L.J. 351 (2004). Kades, Markow, and Misocky primarily address regulation of human antibiotic use and misuse among physicians.

34. Centner, *supra* note 33, at 3-4 (citing Mark Casewell et al., *The European Ban on Growth-Promoting Antibiotics and Emerging Consequences for Human and Animal Health*, 52 J. ANTIMICROBIAL CHEMOTHERAPY 159, 160 (2003)) (stating that both over- and underuse of antimicrobial drugs might have animal and human health consequences).

35. Halpern, *supra* note 33, at 406-07.

success of such programs iteratively and to address gaps in scientific knowledge.[36]

This Article begins with an overview of the science, focusing on processes that lead to antimicrobial resistance. It then reviews current U.S. laws and regulations pertaining to nontherapeutic use of antimicrobials in livestock and to surveillance of antimicrobial-resistant pathogens of food-animal origin. Next, the Article discusses key features of recent U.S. regulatory and legislative efforts, particularly FDA Draft Guidance #209,[37] the Preservation of Antibiotics for Medical Treatment Act (PAMTA) of 2011,[38] and the Strategies to Address Antimicrobial Resistance (STAAR) Act of 2009.[39] Finally, a comparison of regulatory efforts in the United States and Europe is provided, with an emphasis on the scientific evidence for public health success or failure of these policy interventions. The Article concludes with a discussion of how the science of antimicrobial resistance can better inform regulatory efforts in the United States and global efforts to address it. Recommendations for combined regulatory, surveillance, and research strategies are offered, with a focus on evidence-based strategies that are designed to benefit both human and animal health.

II. OVERVIEW OF ANTIMICROBIAL RESISTANCE

While microorganisms may produce antibacterial chemicals naturally,[40] the first documented use of antimicrobial agents by humans was in Egypt in the sixteenth century B.C.[41] Mass production of the first antibiotic, penicillin, began in 1941 to treat wounded soldiers during World War II.[42] The use of antimicrobials quickly became common in both humans and animals to reduce morbidity and suffering by speeding recovery from infection and to cure patients whose natural immune

36. For further discussion, see Roland Schenkel, *The Challenge of Feeding Scientific Advice into Policy-Making*, 330 SCIENCE 1749 (2010) (highlighting strengths and challenges of creating science-based policy).

37. CTR. FOR VETERINARY MED., FDA, DRAFT GUIDANCE #209, THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS (June 28, 2010), http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf.

38. S. 1211, 112th Cong. (2011); H.R. 965, 112th Cong. (2011).

39. H.R. 2400, 111th Cong. (2009).

40. Richard H. Baltz, *Renaissance in Antibacterial Discovery from Actinomycetes*, 8 CURRENT OPINION PHARMACOLOGY 557, 557 (2008).

41. Richard D. Forrest, *Early History of Wound Treatment*, 75 J. ROYAL SOC'Y MED. 198, 198-200 (1982) (describing uses of copper, mercury, honey, and resins).

42. Kathleen Keyes et al., *Antibiotics: Mode of Action, Mechanisms of Resistance, and Transfer*, *in* MICROBIAL FOOD SAFETY IN ANIMAL AGRICULTURE: CURRENT TOPICS 45, 45 (Mary E. Torrence & Richard E. Isaacson eds., 2003).

response alone could not eliminate an infection.[43] As use of antimicrobials became more common, so too did selection for organisms resistant to them.

A. Selection for Resistance

Because of the abundant natural sources of antibiotic substances within ecosystems, resistance to antibiotics predates human use of antimicrobial chemicals by many millennia.[44] Antimicrobial resistance in any given microbe may develop through a process of genetic exchange or mutation, where acquisition of a resistance gene or changes to the bacteria's genetic code provide a mechanism for a given bacterium to survive in the presence of a given antimicrobial or group of antimicrobial drugs.[45] The basic mechanisms of antimicrobial resistance are, in most cases, well-understood.[46] Antimicrobials typically attack one of four bacterial targets: peptidoglycans important to the structure of bacterial cell walls, ribosomes that synthesize important bacterial proteins, enzymes involved in bacterial genome replication, or bacterial cytoplasmic membranes.[47] Resistance genes encode proteins that allow bacteria to evade attack, typically by providing target-specific evasion from the antimicrobial, by inactivating the drug, or by removing the drug from the bacterium.[48] Therefore, in the presence of an antimicrobial chemical, a susceptible bacterium will die and a resistant bacterium will survive to reproduce. As a result, resistant strains will quickly dominate the population of bacteria present in a human, an animal, or the environment.[49] This process is known as "selection."[50]

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43. *Id.* at 45-46.

44. Vanessa M. D'Costa et al., *Antibiotic Resistance Is Ancient*, 477 NATURE 457, 457 (2011).

45. Keyes et al., *supra* note 42, at 46-47.

46. *See* Guardabassi & Courvalin, *supra* note 2.

47. *Id.* at 8-12.

48. *See id.* at 14. Mechanisms of resistance vary among bacteria according to the specific antibiotic or class of antimicrobials under consideration. For example, the *mecA* gene in *Staphylococcus aureus*, making this pathogen methicillin-resistant (MRSA), alters a target protein normally used by the class of penicillin drugs (including methicillin) to inhibit cell wall synthesis. This altered protein, PBP2a, does not bind well to penicillin drugs, and thus MRSA evades penicillin attack. *Id.* (citing CHRISTOPHER WALSH, ANTIBIOTICS: ACTIONS, ORIGINS, RESISTANCE (2003)).

49. Gerard D. Wright, *The Antibiotic Resistome: The Nexus of Chemical and Genetic Diversity*, 5 NATURE REV. MICROBIOLOGY 175, 183-84 (2007).

50. Keyes et al., *supra* note 42, at 51.

Bacteria may acquire genes for antimicrobial resistance from other bacteria through a process called "horizontal gene transfer."[51] Such transfers can occur between bacteria of different species.[52] An example is the acquisition of the *vanA* gene, which confers resistance to the critically important antibiotic vancomycin, by methicillin-resistant *Staphylococcus aureus* (the "superbug" MRSA) from vancomycin-resistant *Enterococcus* (VRE, another "superbug").[53] Of clinical concern, multiple resistance genes may travel together, conferring multidrug resistance with a single genetic transfer event.[54]

Just as humans may live together in communities, so too do microbes, including both "good" commensal bacteria that do not cause disease and "bad" pathogens.[55] Such communities are termed "microbiomes," and the environments in which these microbes live are "microbial ecosystems."[56] The concept of the ecosystem, in which all living beings and nonliving constituents of an area influence each other,[57] is important to understanding how antimicrobial drugs influence bacterial communities.[58] An example of a microbiome is the collection of microorganisms that comprise the human intestinal flora, and this population of bacteria and other microbes plays an important role in digestion and other gastrointestinal functions.[59]

Microbial ecosystems are dynamic; they change in response to new components.[60] A small number of resistant bacteria in a microbiome may occur through natural processes, such as mutation.[61] However, when antimicrobials are added to a microbial ecosystem (e.g., by administering drugs to sick humans or by feeding antimicrobials to broiler chickens in

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51. This typically occurs on a mobile genetic element (e.g., plasmid), which is a piece of genetic material capable of being transferred between bacteria, usually via a process called bacterial conjugation. *See* Guardabassi & Courvalin, *supra* note 2, at 1.

52. Teruyo Ito et al., *Insights on Antibiotic Resistance of* Staphylococcus Aureus *from Its Whole Genome: Genomic Island SCC*, 6 DRUG RESISTANCE UPDATES 41, 49 (2003).

53. *Id.* at 41, 49.

54. Wright, *supra* note 49, at 176.

55. Les Dethlefsen et al., *An Ecological and Evolutionary Perspective on Human-Microbe Mutualism and Disease*, 449 NATURE 811, 811-12 (2007).

56. Meghan F. Davis et al., *An Ecological Perspective on U.S. Industrial Poultry Production: The Role of Anthropogenic Ecosystems on the Emergence of Drug-Resistant Bacteria from Agricultural Environments*, 14 CURRENT OPINION MICROBIOLOGY 244, 244-45 (2011).

57. Michel Loreau, *Linking Biodiversity and Ecosystems: Towards a Unifying Ecological Theory*, 365 PHIL. TRANSACTIONS ROYAL SOC'Y B 49, 49 (2010).

58. *See* Davis et al., *supra* note 56, at 244-45.

59. Peter J. Turnbaugh et al., *The Human Microbiome Project*, 449 NATURE 804, 805 (2007).

60. Davis et al., *supra* note 56, at 244-45.

61. *See* Wright, *supra* note 49, at 176-77.

an industrial poultry production environment), these drugs increase selective pressure in the feed itself, in the animal's intestine, and in the manure or litter. This, in turn, may drive increases in the populations of resistant bacteria.[62] As resistant bacteria multiply, the number of genes for resistance also multiplies.[63] The sum of all the diverse genes for resistance in a community of microbes is called the "resistome," or reservoir of resistance.[64] When a new bacterium, such as a pathogen, enters a microbial community under the influence of antimicrobials, it may more easily acquire the "information," or resistance gene, that will allow it to survive.[65] Even a "good" bacterium may develop resistance and transfer this information to a pathogen, making consideration for resistance in both commensal and pathogenic bacteria (i.e., consideration of the entire resistome) important to any discussion of antimicrobial regulation.[66] Further, resistant bacteria may protect susceptible members of their microbial community (including potential pathogens) from antimicrobial effects, although the mechanisms of such "altruistic" behavior are not yet well characterized.[67] This underscores the importance of considering entire microbial communities, not just specific pathogens, in designing strategies to retain clinical efficacy of antimicrobial agents.

B. Judicious Use

Physicians and researchers typically have associated the recent increase in infections caused by drug-resistant pathogens with poor medical practices and overuse of antimicrobials in the environment of a hospital or clinic.[68] Hospital environments may promote selection for

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62. *Id.*

63. Multiplication of resistance genes may occur through expansion of resistant populations of bacteria (one resistant bacterium becomes two, etc.) and also through horizontal gene transfer, in which the plasmid that contains the gene itself is copied and shared with a formerly susceptible bacterium. *Id.* at 183.

64. *Id.* at 178 (citing Vanessa M. D'Costa et al., *Sampling the Antibiotic Resistome*, 311 SCIENCE 374 (2006)).

65. Davis et al., *supra* note 56, at 246 & fig.2, 247; Elizabeth Skippington & Mark A. Ragan, *Lateral Genetic Transfer and the Construction of Genetic Exchange Communities*, 35 FEMS MICROBIOLOGY REV. 707, 715 (2011).

66. Henry H. Lee et al., *Bacterial Charity Work Leads to Population-Wide Resistance*, 467 NATURE 82, 83 (2010).

67. *Id.*

68. Ellen K. Silbergeld et al., *One Reservoir: Redefining the Community Origins of Antimicrobial-Resistant Infections*, 92 MED. CLINICS N. AM. 1391, 1391-92 (2008) (citing RAMANAN LAXMINARAYAN ET AL., EXTENDING THE CURE: POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE (2007), *available at* http://www.rwjf.org/files/research/etc fullreport.pdf).

and transmission of resistant bacteria.[69] To help reduce this phenomenon, good medical practice dictates that a patient who is infected with a resistant organism should be identified through medical follow-up, and another antimicrobial drug should be prescribed to effectively eliminate the resistant organism.[70] The following hypothetical example illustrates this practice: Sam enters an outpatient clinic because she has developed an abscess on her hand following a sports injury. Her physician cultures the wound and starts Sam on amoxicillin, a type of antimicrobial related to penicillin. Two days later, the laboratory reports that the wound is infected with methicillin-resistant *Staphylococcus aureus* (MRSA), a microbe resistant to the entire beta-lactam class of antimicrobials that includes penicillin. In light of this information, Sam's physician follows up with her and prescribes clindamycin, an antimicrobial more likely to treat the infection based on the resistance profile (i.e., culture and sensitivity report) provided by the laboratory. This is an example of "antimicrobial stewardship" or "judicious use."[71]

Veterinary use of antimicrobials to treat clinical infection in individual animals, such as pets,[72] also falls under judicious use guidelines similar to those employed by physicians who treat humans.[73] For treatment of an individual animal, a veterinarian may follow a similar model as presented above, seeking laboratory culture and sensitivity testing of suspected infections.[74] For food-producing animals, a veterinarian instead may seek laboratory confirmation of a suspected disease by testing a representative sample of animals in the flock, school, or herd.[75] Antimicrobial use in livestock may be under veterinary supervision to treat a diagnosed infection, and drugs for disease

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69. *See* Axel Kola et al., *Is There an Association Between Nosocomial Infection Rates and Bacterial Cross Transmissions?*, 38 CRITICAL CARE MED. 46 (2010); Neil Fishman, *Antimicrobial Stewardship*, 119(6A) AM. J. MED. S53 (2006).

70. *See* Timothy H. Dellit et al., *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program To Enhance Antimicrobial Stewardship*, 44 CLINICAL INFECTIOUS DISEASES 159, 167 (2007). *See generally Get Smart: Know When Antibiotics Work*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/getsmart/index.html (last updated Mar. 6, 2012).

71. *See* Dellit et al., *supra* note 70, at 159-60.

72. Pets, or companion animals, include dogs, cats, horses, rabbits, and other animals that might be kept in or near the household.

73. *Issues: Judicious Therapeutic Use of Antimicrobials*, AM. VETERINARY MED. ASS'N, http://www.avma.org/issues/policy/jtua.asp (last visited Mar. 21, 2012).

74. *Id.*

75. *See* O.M. RADOSTITS ET AL., HERD HEALTH: FOOD ANIMAL PRODUCTION MEDICINE 15 (2d ed. 1994).

treatment often are administered by injection.[76] The majority of antimicrobial use in food-producing animals in the United States, however, is not for disease treatment but, instead, for growth promotion or other purposes.[77] Without needing a veterinary prescription, food animal producers can purchase antimicrobial supplements to add to the feed of the animals they raise for either growth promotion purposes or for prevention of disease in animals exposed to pathogens (termed "prophylaxis").[78]

C. Antimicrobials as Pollutants

Antimicrobial use at nontherapeutic levels in food-producing animals (livestock), primarily for growth promotion,[79] is of increasing concern.[80] Because food-producing animals excrete 75% of the antimicrobials they consume unchanged or as active metabolites of the drug,[81] antimicrobials not only apply selective pressure on the intestinal microbial community of the food-producing animal, but also on the microbiome of the animal's environment, such as the barn, pasture, and fields where manure is applied.[82] Spillage of medicated feed may contaminate local soils and waters.[83] The presence of antimicrobial drugs from these sources can influence the local microbial ecology, allowing resistant organisms to survive and to become more common in bacterial communities in and around concentrated animal feeding operations

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76. *See id.* at 85. Parenteral use (injection) is common for disease treatment except some uses in poultry production and aquaculture due to difficulty of injection or the muscle damage an injection could cause in these smaller species. *Id.*

77. *See* Prescott, *supra* note 9, at 22.

78. *FDA Reports to Slaughter: Over 70 Percent of Antibiotics Administered to Animals in Feed*, CONGRESSWOMAN LOUISE M. SLAUGHTER, http://www.slaughter.house.gov/index.php?option=com_content&task=view&id=2481&Itemid=100065 (last visited Mar. 21, 2012) (indicating that most antimicrobial use in food animals is via medicated feed or water); David C. Love et al., *Dose Imprecision and Resistance: Free-Choice Medicated Feeds in Industrial Food Animal Production in the United States*, 119 ENVTL. HEALTH PERSP. 279, 279-80 (2011).

79. In addition to medication of animals, antimicrobials also may be used in agricultural environments, in environmental sanitation, and crop treatment; these latter uses are regulated by the Environmental Protection Agency. *Pesticide Registration Manual: Chapter 18—Other Federal or State Agency Requirements*, U.S. ENVTL. PROT. AGENCY, http://www.epa.gov/pesticides/bluebook/chapter18.html#antimicrobial (last updated Dec. 28, 2011).

80. *See* WHO, *supra* note 20, at 1-2; McEwen & Fedorka-Cray, *supra* note 10, at S97.

81. *See* G. Keith Elmund et al., *Role of Excreted Chlortetracycline in Modifying the Decomposition Process in Feedlot Waste*, 6 BULL. ENVTL. CONTAMINATION & TOXICOLOGY 129, 131 (1971).

82. Davis et al., *supra* note 56, at 246-48.

83. Love et al., *supra* note 78, at 279.

(CAFOs).[84] Further, the CAFO environment,[85] marked by crowding of animals in small, often indoor spaces, intensifies the spread of bacteria among animals and increases pathogen contamination of their barns or pens.[86] This led scientist Dr. Jose Luis Martinez to coin the term "antibiotic pollution," which may refer to either the antimicrobial chemicals themselves (which, like other chemical pollutants, may degrade over time) or the resistance genes they foster (which may, in fact, multiply through horizontal gene transfer and reproduction of resistant bacteria).[87] Residents of rural communities may be exposed to antimicrobial pollution through air and water contaminated by manure waste,[88] and consumers nationwide (and globally) can be exposed through the retail meat,[89] seafood,[90] or other products they contact, such as fertilizer derived from contaminated animal products.[91]

Both national surveillance and independent research data support the existence of these pathways of exposure to resistant pathogens and

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84. *See* B. Halling-Sørensen et al., *Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment—A Review*, 36 CHEMOSPHERE 357, 359 fig.1 (1997); Gitte Sengeløv et al., *Bacterial Antibiotic Resistance Levels in Danish Farmland as a Result of Treatment with Pig Manure Slurry*, 28 ENV'T INT'L 587, 590-92 (2003); *see also* Moussa S. Diarra et al., *Impact of Feed Supplementation with Antimicrobial Agents on Growth Performance of Broiler Chickens,* Clostridim Perfringens *and* Enterococcus *Counts, and Antibiotic Resistance Phenotypes and Distribution of Antimicrobial Resistance Determinants in* Escherichia Coli *Isolates*, 73 APPLIED & ENVTL. MICROBIOLOGY 6566 (2007).

85. CAFOs, otherwise known as industrial food animal production facilities, are typified by high-throughput methods designed to achieve a uniform product (meat, milk, or eggs) in a standardized period of time to accommodate mechanized harvest methods. High animal density, waste (manure) concentration, and use of antimicrobials, often in medicated feed, are hallmarks of these systems. *See* Davis et al., *supra* note 56; Love et al., *supra* note 78; Silbergeld et al., *supra* note 10, at 152-53.

86. Silbergeld et al., *supra* note 10, at 153.

87. Jose Luis Martinez, *Environmental Pollution by Antibiotics and by Antibiotic Resistance Determinants*, 157 ENVTL. POLLUTION 2893, 2893-94 (2009).

88. Davis et al., *supra* note 56, at 247; Jay P. Graham & Keeve E. Nachman, *Managing Waste from Confined Animal Feeding Operations in the United States: The Need for Sanitary Reform*, 8 J. WATER & HEALTH 646, 654 (2010); Amy Chapin et al., *Airborne Multidrug-Resistant Bacteria Isolated from a Concentrated Swine Feeding Operation*, 113 ENVTL. HEALTH PERSP. 137, 137 (2005).

89. FDA, NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM: 2008 EXECUTIVE REPORT 1 (2011), http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM253024.pdf; *see* McEwen & Fedorka-Cray, *supra* note 10, at S100.

90. *See* David C. Love et al., *Veterinary Drug Residues in Seafood Inspected by the European Union, United States, Canada, and Japan from 2000 to 2009*, 45 ENVTL. SCI. & TECH. 7232 (2011).

91. D.C. Love et al., *Feather Meal: A Previously Unrecognized Route for Reentry into the Food Supply of Multiple Pharmaceuticals and Personal Care Products (PPCPs)*, 46 ENVTL. SCI. & TECH. 3975 (2012).

genes for resistance.[92] Antimicrobial resistance patterns in bacteria cultured from humans have been shown to follow resistance trends in food and food-producing animals for bacteria that can be transmitted between animals and humans, termed "zoonoses."[93] In the United States, studies have reported that resistance genes and resistant *Salmonella* bacteria from food-producing animals matched those found in humans.[94] Similar associations for ceftiofur resistance[95] were identified in a national surveillance program, the National Antimicrobial Resistance Monitoring System (NARMS),[96] which is a joint effort of the FDA, the Centers for Disease Control and Prevention (CDC), and the United States Department of Agriculture (USDA).[97] Food is an important route for

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92. Frank M. Aarestrup et al., *Resistance in Bacteria of the Food Chain: Epidemiology and Control Strategies*, 6 EXPERT REV. ANTI-INFECTIVE THERAPY 733, 737-38 (2008); Scott A. McEwen et al., Letter to the Editor, *Antibiotics and Poultry—A Comment*, 51 CAN. VETERINARY J. 561 (2010).

93. *See* FDA, *supra* note 89; Viroj Wiwanitkit, Letter to the Editor, *New H1N1 Influenza Virus Infection: Focus on Humans and Animals Interface—A Comment*, 51 CAN. VETERINARY J. 561 (2010) (citing James O. Lloyd-Smith et al., *Epidemic Dynamics at the Human-Animal Interface*, 326 SCIENCE 1362 (2009)). Effects from use of fluoroquinolones, virginiamycin, and other drugs will be discussed *infra* Parts III.F and V.A.

94. Nkuchia M. M'ikanatha et al., *Multidrug-Resistant* Salmonella *Isolates from Retail Chicken Meat Compared with Human Clinical Isolates*, 7 FOODBORNE PATHOGENS & DISEASE 929 (2010); Kimberly A. Alexander et al., *Antimicrobial Resistant* Salmonella *in Dairy Cattle in the United States*, 33 VETERINARY RES. COMM. 191, 191 (2009).

95. Of note, the finding of an association between use of cephalosporins, including ceftiofur, in food-producing animals and cephalosporin resistance in human isolates was the basis for an attempt by the FDA to restrict extralabel use of these antimicrobials in food-producing animals. New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition, 73 Fed. Reg. 38,110, 38,110 (July 3, 2008) (to be codified at 21 C.F.R. pt. 530). The initial order was revoked before it took effect. *FDA Revokes Order Prohibiting Extralabel Use of Cephalosporin*, U.S. FOOD & DRUG ADMIN. (Nov. 25, 2008), http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm054431.htm. A new order to prohibit certain extralabel use of certain cephalosporins was published in early 2012. New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition, 77 Fed. Reg. 735 (Jan. 6, 2012) (to be codified at 21 C.F.R. pt. 530). Extralabel use by veterinarians is use in a species, at a dosage, or via a route not specifically included in the approval (label) of that animal drug. The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994, as implemented by FDA regulation (21 C.F.R. § 530 (2011)), authorizes the veterinarian to prescribe an animal drug for extralabel use under certain conditions. 21 C.F.R. § 530.1. This extralabel use is, in part, a response to the many species veterinarians need to treat which may not have specifically been tested during the drug approval process.

96. CTRS. FOR DISEASE CONTROL & PREVENTION & FDA, NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM: ENTERIC BACTERIA—2004, HUMAN ISOLATES FINAL REPORT 8-9 (2007), http://www.cdc.gov/narms/annual/2004/NARMSAnnualReport2004.pdf.

97. *Hearing To Review the Advances of Animal Health Within the Livestock Industry: Hearing Before the Subcomm. on Livestock, Dairy & Poultry of the H. Comm. on Agric.*, 110th Cong. 16 (2008) (statement of Bernadette Dunham, Director, Center for Veterinary Medicine, FDA).

transmission of zoonotic pathogens from food-producing animals to humans because of its broad impact on potentially all citizens.[98]

III. THE REGULATION OF ANTIMICROBIALS IN THE UNITED STATES

Antimicrobial resistance has threatened human health in the United States and globally for over half a century.[99] Although federal agencies first proposed restriction of antimicrobial use in food animals in 1977,[100] the first enforceable action to limit such use did not take place for almost three decades.[101] Federal efforts to combat antimicrobial resistance can be divided into three broad categories: programs to support research and surveillance of antibiotic resistance to better describe the problem,[102] guidance statements for industry to inform self-regulation and best management practices,[103] and bans, restrictions, or approval limitations for antimicrobial use in food-producing animals.[104]

Veterinary antimicrobials, like those intended for use in humans, are regulated by the FDA through delegated authority from the Federal Food, Drug, and Cosmetic Act.[105] Most limitations on use of veterinary antimicrobials occur through the drug approval process. Before drug companies can market a new animal drug (including antimicrobials), the FDA must review scientific documentation on the safety and efficacy of the drug's proposed use and approve its label, which contains information about doses, species, and indications for use.[106] Many antimicrobials administered for nontherapeutic use in medicated animal feed received

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98. *See* Charles P. Gerba & James E. Smith, Jr., *Sources of Pathogenic Microorganisms and Their Fate During Land Application of Wastes*, 34 J. ENVTL. QUALITY 42, 42 (2005). Even vegetarians and vegans may be impacted by zoonotic bacteria through the food they eat because vegetables may be contaminated by water or dust containing bacteria of food animal origin. Examples include *E. coli* 0157:H7 outbreaks traced to animal manure spread in apple orchards and irrigation water for spinach crops. *Id.* at 43 & tbl.2, 44 (citing J.E. Smith & J.M. Perdek, *Assessment and Management of Watershed Microbial Contaminants*, 34 CRITICAL REV. ENVTL. SCI. & TECH. 109 (2004)).

99. *See* J.C. Sherris & M.E. Florey, Editorial, *Relation of Penicillin Sensitivity in Staphylococci to Clinical Manifestations of Infection*, 1 LANCET 309, 311 (1951).

100. Stanley Falkow & Donald Kennedy, *Antibiotics, Animals, and People—Again!*, 291 SCIENCE 397, 397 (2001).

101. 21 C.F.R. §§ 520, 556 (2005) (concerning the withdrawal of FDA approval for uses in poultry of veterinary fluoroquinolones).

102. *See* 42 U.S.C. § 247d-5 (2006).

103. *See* CTR. FOR VETERINARY MED., *supra* note 30.

104. Oral Dosage Form: New Animal Drugs, 21 C.F.R. § 520 (2011); Tolerances for Residues of New Animal Drugs in Food, 21 C.F.R. § 556.

105. 21 U.S.C. §§ 301-399 (2006).

106. *Id.* § 360b(a).

FDA approval by the early 1970s.[107] However, federal documents outline concerns with promotion of antimicrobial resistance from approved veterinary drugs in food-producing animals as early as the 1970s.[108] Selection for resistance by approved antimicrobials, particularly with increases in drug use, indicates the importance of public health monitoring for antimicrobial resistance after a drug has been approved.

Research and surveillance efforts through NARMS provide information that may inform additional, postapproval regulation of antimicrobials, but do not provide a legal mechanism to restrict use of the drugs.[109] In the past two decades, regulations have been promulgated and bills have been introduced to provide additional oversight of veterinary and human antimicrobial use in the United States.[110] The NARMS surveillance program, begun in 1996, was strengthened in 1997 through the President's Food Safety Initiative (FSI).[111] The FSI introduced risk assessment[112] as a tool to address the potential for animal drugs to promote antimicrobial resistance. This was later formalized in the "Framework Document"[113] that became FDA Guidance #152.[114] The 1997 FSI led to the formation of the President's Council on Food Safety in 1998,[115] which then appointed the Interagency Task Force on Antimicrobial Resistance in 1999.[116] In 2010, the FDA offered Draft

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107. *See* J.S. Kiser et al., *Antibiotics as Feedstuff Additives: The Risk-Benefit Equation for Man*, 1 CRC CRITICAL REV. TOXICOLOGY 55, 55-56 (1971); J.S. Kiser, *A Perspective on the Use of Antibiotics in Animal Feeds*, 42 J. ANIMAL SCI. 1058, 1061-63 (1976); Prescott, *supra* note 9, at 24 tbl.2 (describing the first FDA task force (1972) on use of antibiotics in animal feeds, which cited public health concerns with promotion of resistance).

108. L. Tollefson et al., *Therapeutic Antibiotics in Animal Feeds and Antibiotic Resistance*, 16 SCI. & TECHNICAL REV. 709, 709-10 (1997) (citing K.S. Crump, *Estimating Human Risks from Drug Feed Additives*, *in* 2 DRUGS IN LIVESTOCK FEED (1979)) (noting concerns with food animal use of antimicrobials, particularly in animal feed).

109. *See* FDA, *supra* note 89, at 1-2.

110. *See infra* Appendix I: Regulatory Timeline.

111. President's National Food Safety Initiative, 62 Fed. Reg. 13,589, 13,590 (Mar. 21, 1997) (improving coordination among agencies by clarifying their roles in prevention and emergence of resistant pathogens).

112. Risk assessment is a process used by government agencies and other groups, including industry, to characterize and quantify hazards associated with certain activities. Originally designed for assessment of toxicants, risk assessment more recently has been applied to hazards of microbial origin, including concerns with antimicrobial resistance.

113. *A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*, U.S. FOOD & DRUG ADMIN., www.fda.gov/downloads/animalveterinary/newsevents/cvmupdates/ucm134323.pdf (last visited Mar. 22, 2012).

114. CTR. FOR VETERINARY MED., *supra* note 30.

115. Exec. Order No. 13,100, 3 C.F.R. § 209 (1999).

116. *Antibiotic/Antimicrobial Resistance: Interagency Task Force on Antimicrobial Resistance*, CENTERS FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/drugresistance/actionplan/taskforce.html (last updated Feb. 3, 2012); *see NARMS Program*, U.S. FOOD & DRUG

Guidance #209 as a formal statement of its opinion that the use of antimicrobials to promote growth in food-producing animals runs counter to public health goals.[117] Two bills, the Strategies to Address Antimicrobial Resistance (STAAR) Act[118] and the Preservation of Antimicrobials for Medical Treatment (PAMTA) Act of 2007,[119] which would provide additional mechanisms of regulation, have been introduced multiple times in the past decade.[120] The following Parts provide additional description of these key programs, guidance documents, and bills related to the regulation of antimicrobial use in food animals.

A. National Antimicrobial Resistance Monitoring Program

The National Antimicrobial Resistance Monitoring Program (NARMS), part of the Emerging Infections Program, was launched in 1996 as a surveillance program for antimicrobial resistance in foodborne pathogens.[121] This was a multiagency effort involving, within the USDA, the Food Safety and Inspection Service (FSIS), Agricultural Research Service (ARS), and Animal and Plant Health Inspection Service (APHIS); and, within the Department of Health and Human Services (HHS), the FDA, including the Center for Veterinary Medicine (CVM), and the CDC.[122] Specifically, NARMS microbiologists test four groups of foodborne bacteria—*Salmonella*, *Campylobacter*, *Enterococcus*, and *E. coli*[123]—for resistance to certain antimicrobials, they bank strains for future testing, and they perform molecular strain typing of certain

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ADMIN., http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059089.htm (last updated Sept. 8, 2010).

117. CTR. FOR VETERINARY MED., *supra* note 37, at 4.

118. H.R. 2400, 111th Cong. (2009).

119. H.R. 962, 110th Cong. (2007).

120. *See* Preservation of Antibiotics for Medical Treatment Act of 2011, H.R. 965, 112th Cong. (2011); Preservation of Antibiotics for Medical Treatment Act of 2011, S. 1211, 112th Cong. (2011).

121. *Hearing To Review the Advances of Animal Health Within the Livestock Industry: Hearing Before the Subcomm. on Livestock, Dairy & Poultry of the H. Comm. on Agric.*, *supra* note 97, at 16-17.

122. USDA & U.S. DEP'T OF HEALTH & HUMAN SERVS., USDA/HHS RESPONSE TO THE HOUSE AND SENATE REPORTS: AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS BILL, 2000—ANTIBIOTIC RESISTANCE IN LIVESTOCK 1 (Sept. 14, 2000), http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/UCM134733.pdf.

123. FDA, *supra* note 89, at 1. *Salmonella spp.* and *Campylobacter jejuni* are human enteric pathogens, while *Enterococcus* and *E. coli* may be present commensally or may cause disease opportunistically. *Id.*

isolates.[124] This work currently is implemented in a growing number of states that comprise the FoodNet surveillance program for diseases of foodborne origin.[125] Currently, NARMS is an umbrella program for three distinct entities: PulseNet (CDC), the "human arm" of the program which is a database of isolates from human foodborne infections; VetNet (USDA), the "animal arm" of the program which parallels PulseNet for isolates of animal origin; and the "retail arm," which is an active surveillance program for meats from federally inspected slaughterhouses and is a collaboration between the CVM, the CDC, and FoodNet, although most of the laboratory work is performed by branches of the USDA.[126]

As the primary surveillance network for antimicrobial resistance of animal origin, NARMS is limited in its focus on antimicrobial resistance in foodborne bacteria. While food is an important pathway for transmission of zoonotic diseases between animals and humans, other pathways, such as occupational health risks and rural community exposure to industrial agricultural environments, are not captured by this surveillance system.[127] Despite these limitations, NARMS exemplifies recent governmental success to improve surveillance for antimicrobial-resistant pathogens. It was strengthened in the past decade, not only through the 1997 FSI, but also through the work of a collaborative interagency task force, detailed next, which added VetNet, and expanded the testing program for retail meat products.[128]

B. A Public Health Action Plan To Combat Antimicrobial Resistance

In 1999, the U.S. government convened the Interagency Task Force on Antimicrobial Resistance (Task Force) in response to a February 25

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124. The antimicrobials are: Azithromycin, Ciprofloxacin, Clindamycin, Erythromycin, Florfenicol, Gentamicin, Nalidixic Acid, Telithromycin, and Tetracycline. *Id.* at 5.

125. FoodNet was launched with five states, and additional states were added slowly through a state application/selection process. The current FoodNet states are Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, California (selected counties), Colorado (selected counties), and New York (selected counties). *See* Samantha Yang, *FoodNet and Enter-net: Emerging Surveillance Programs for Foodborne Diseases*, 4 EMERGING INFECTIOUS DISEASES 457 (1998); *FoodNet—Foodborne Diseases Active Surveillance Network*, CENTERS FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/foodnet/ (last modified Feb. 28, 2012).

126. *NARMS Program*, *supra* note 116; *see* FDA, *supra* note 89, at 1.

127. *See NARMS Program*, *supra* note 116.

128. *Progress Report: Implementation of a Public Health Action Plan To Combat Antimicrobial Resistance—Progress Through 2007*, at 3, 19, CENTERS FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/drugresistance/actionplan/2007_report/ann_rept.pdf (last visited Mar. 22, 2012).

congressional hearing.[129] The goal was to unify strategies among the disparate federal agencies to reduce the burden of antimicrobial resistance and relieve the impacts of antimicrobial resistance on human health.[130] Three agencies—the CDC, the FDA, and the National Institutes of Health (NIH)—were assigned to jointly chair the Task Force.[131] Additional members of the Task Force included the USDA and the Environmental Protection Agency (EPA), among others.[132]

The Task Force published *A Public Health Action Plan To Combat Antimicrobial Resistance* (*Action Plan*) in 2001.[133] This document and its 2011 update[134] detailed the domestic and international goals of U.S. federal agencies with regard to antimicrobial resistance and use of antimicrobials in humans and animals. A key recommendation was to "[m]onitor [antimicrobial resistance] in agricultural settings to protect the public's health by ensuring a safe food supply as well as animal and plant health."[135] Policy recommendations,[136] as described in the *Action Plan*,

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129. *Antibiotic/Antimicrobial Resistance: Interagency Task Force on Antimicrobial Resistance*, CENTERS FOR DISEASE CONTROL & PREVENTION, www.cdc.gov/drugresistance/actionplan/taskforce.html (last updated Feb. 3, 2012); *Antimicrobial Resistance: Solutions for this Growing Public Health Threat: Hearing Before the Subcomm. on Pub. Health of the S. Comm. on Health, Educ., Labor, and Pensions*, 106th Cong. 33-36 (1999) (statement of James M. Hughes, Director, National Center for Infectious Diseases, Centers for Disease Control and Prevention). The Task Force began work before formal congressional action to organize and fund the task force. *See* Abigail Colson, *The Interagency Task Force on Antimicrobial Resistance: 10 Years of Coordinated Federal Action*, at 2 (Extending the Cure, Policy Brief 9, May 2010), http://www.extendingthecure.org/sites/default/files/Policy%20Brief%209.pdf. H.R. 2498, the bill that established the task force, became law in 2000. *Id.*

130. Interagency Task Force on Antimicrobial Resistance, *A Public Health Action Plan To Combat Antimicrobial Resistance* 2, CENTERS FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/drugresistance/actionplan/aractionplan-archived.pdf (last visited Mar. 22, 2012) (archival version of the action plan).

131. *Id.*

132. Interagency Task Force on Antimicrobial Resistance (ITFAR): An Update on a Public Health Action Plan To Combat Antimicrobial Resistance, 76 Fed. Reg. 63,927, 63,927 (Oct. 14, 2011). Initial members included the Agency for Healthcare Research and Quality, the Health Care Financing Administration, the Health Resources and Services Administration, the Department of Agriculture, the Department of Defense, and the Department of Veterans Affairs. Interagency Task Force on Antimicrobial Resistance, *supra* note 130. Later, the Centers for Medicare and Medicaid Services and the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response were added. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE, A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE, at i (2011), http://www.cdc.gov/drugresistance/pdf/public-health-action-plan-combat-antimicrobial-resistance.pdf.

133. Interagency Task Force on Antimicrobial Resistance, *supra* note 130.

134. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE, *supra* note 132.

135. Interagency Task Force on Antimicrobial Resistance, *supra* note 130, at 3.

136. Stakeholders have commented, "The task force would be an ideal body to craft strategy, guiding instead of merely documenting federal action on antimicrobial resistance. However, it has largely left that role untouched." Colson, *supra* note 129, at 3.

were to be "implemented incrementally, dependent on the availability of resources" by each of the key stakeholders (i.e., federal agencies) involved in crafting the document.[137] Although it encouraged additional regulatory action on the part of agencies, the document itself neither provided a legal mandate for enforcement nor any penalty for noncompliance.[138]

To date, this collaborative effort has led to the initiation or enhancement of a number of projects involved in controlling antimicrobial resistance, including the expansion of the NARMS surveillance network as previously described,[139] mandates for new research on use of antimicrobials in food-producing animals as part of the USDA's National Animal Health Monitoring System (NAHMS),[140] and an evaluation of fluoroquinolone resistance from poultry and poultry products[141] that led to a later FDA ban on fluoroquinolone use in poultry.[142] Surveillance systems beyond NARMS have been bolstered, including the National Healthcare Safety Network (NHSN), although this latter program focuses exclusively on infections in healthcare settings and is not currently linked to animal monitoring systems.[143] A USDA program, the Collaboration in Animal Health, Food Safety, and Epidemiology, was developed to track *Salmonella*, *Campylobacter*, *E. coli*, and Enterococci on sentinel swine farms, and to conduct pilot programs in New York state and the Midwest for dairy herd risk assessment.[144]

In the past decade, nongovernmental stakeholders have criticized the Task Force for its lack of progress towards implementation of some of the goals outlined in the *Action Plan*.[145] In *Hogging It!*, the Union of

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137. Interagency Task Force on Antimicrobial Resistance, *supra* note 130, at 2.

138. *See id.*

139. *See supra* Part III.A.

140. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE, *supra* note 132, at 17. Some reports are pending publication. *See id.* at 28-30.

141. *Id.* at 14, 17.

142. Animal Drugs, Feeds, and Related Products; Enrofloxacin for Poultry; Withdrawal of Approval of New Animal Drug Application, 70 Fed. Reg. 44,048 (Aug. 1, 2005) (codified at 21 C.F.R. pts. 520 & 556); *see infra* Part III.F.

143. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE, *supra* note 132, at 6. According to a presentation by the Task Force at a public meeting for comment in Washington, D.C., at the time of writing, the Task Force plans to expand NHSN further, including collection of data on geographic distribution of infections in healthcare settings. Interagency Task Force on Antimicrobial Resistance, Presentation for Public Comment (Nov. 15, 2011).

144. *Progress Report: Implementation of a Public Health Action Plan To Combat Antimicrobial Resistance—Progress Through 2007*, *supra* note 128, at 17-18.

145. *See* Ronald N. Jones, *The Emergent Needs for Basic Research, Education, and Surveillance of Antimicrobial Resistance: Problems Facing the Report from the American*

Concerned Scientists (UCS) called for a faster implementation of Priority Action 5 of the *Action Plan*, regarding improved monitoring systems.[146] In addition, UCS has advocated for mandates relating to companies' reports of the quantities and types of antimicrobials employed for therapeutic and nontherapeutic uses as feed additives in greater detail than previously provided.[147] While the Animal Drug User Fee Amendments of 2008, which required the FDA to provide annual summary reports on sale and distribution of antimicrobials for use in food-producing animals,[148] partially succeeded in addressing these concerns, the lack of refinement of the information provided has engendered further criticism.[149] Opposition to implementation of regulatory and research efforts related to the *Action Plan* also has come from the pharmaceutical industry, agribusiness, and allied professionals who may benefit economically from nontherapeutic use of antimicrobials.[150]

A top priority action item in the *Action Plan* was to "refine and implement the proposed FDA framework for approving new antimicrobial drugs for use in food-animal production and, when appropriate, for re-evaluating currently approved veterinary antimicrobial drugs."[151] The following Parts document the FDA's progress toward this goal.

Society for Microbiology Task Force on Antibiotic Resistance, 25 DIAGNOSTIC MICROBIOLOGY & INFECTIOUS DISEASE 153, 153 (1996).

146. MELLON ET AL., *supra* note 17, at 65.

147. *Id.* at 65-66.

148. 21 U.S.C. § 360b(l)(3) (Supp. 2008).

149. *See* Dave Love, *Drug Amounts for Food Animals Now Reported by FDA: Thanks, It's About Time!*, CENTER FOR LIVABLE FUTURE BLOG (Dec. 13, 2010), http://www.livable futureblog.com/2010/12/drug-amounts-for-food-animals-now-reported-by-fda-thanks-it's-about-time (regarding the need to report amounts by specific drug and also by use in food-producing animals).

150. Letter from Am. Ass'n of Avian Pathologists et al. to Michael B. Enzi, Ranking Member, Senate Comm. on Health, Educ., Labor & Pensions (Nov. 18, 2009), http://www.meatami.com/ht/a/GetDocumentAction/i/55364 (urging defeat of the bill); *see* Kennedy, *supra* note 31; *Low-Level Use of Antibiotics in Livestock and Poultry*, FOOD MARKETING INST., http://www.fmi.org/docs/media/bg/antibiotics.pdf (last visited Mar. 22, 2012); Timothy S. Cummings, *Stakeholder Position Paper: Poultry*, 73 PREVENTIVE VETERINARY MED. 209 (2006).

151. Interagency Task Force on Antimicrobial Resistance, *supra* note 130, at 29 (footnote omitted).

C. *FDA Guidance #152*

First proposed in 1998 as the "Framework Document,"[152] the FDA published *Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern* (*FDA Guidance #152*) in 2003.[153] This document provided FDA's recommendation that consideration of indirect effects on human health through antimicrobial resistance pathways be included when evaluating the safety of new animal drugs.[154] *FDA Guidance #152* offers instruction to drug sponsors on conducting qualitative risk assessments for new drugs under consideration for approval to assess their abilities to pose risks to human health through the development of antimicrobial resistance.[155] FDA then uses the submitted risk assessments to inform safety assessments of the drugs in question.

According to the testimony of the Director of the FDA's Center for Veterinary Medicine, Bernadette Dunham, [156] before the House Committee on Agriculture in 2008 and the testimony of Principal Deputy Commissioner for the FDA, Joshua Sharfstein, [157] to the House Committee on Rules in 2009, the FDA has slowly begun voluntary application of these criteria to currently approved antimicrobial drugs. Both Dunham and Sharfstein cited the 2001 *Public Health Action Plan To Combat Antimicrobial Resistance* as a key document guiding this and similar FDA regulatory efforts. However, Guidance #152 was not designed to be legally binding, and the FDA has permitted industry to use alternate methods (other than risk assessment) to assess the microbial food safety of some proposed drugs.[158]

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152. *A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals*, *supra* note 113.

153. CTR. FOR VETERINARY MED., *supra* note 30.

154. *Id.* at 2.

155. *Id.* at 12-13; L. Tollefson, *Developing New Regulatory Approaches to Antimicrobial Safety*, 51 J. VETERINARY MED. SERIES B 415 (2004).

156. *Hearing To Review the Advances of Animal Health Within the Livestock Industry: Hearing Before the Subcomm. on Livestock, Dairy & Poultry of the H. Comm. on Agric.*, *supra* note 97 (statement of Bernadette Dunham).

157. *Preservation of Antibiotics for Medical Treatment Act (PAMTA): Hearing on H.R. 1549 Before the H. Comm. on Rules*, *supra* note 31 (statement of Joshua M. Sharfstein).

158. Alternative methods are not detailed expressly in the document; instead, industry is urged to discuss possible alternatives with FDA officials. CTR. FOR VETERINARY MED., *supra* note 30, at 2-3.

D. FDA Draft Guidance #209

In June 2010, the FDA issued Draft Guidance #209.[159] In this document, the FDA stated that it "believes the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health."[160] Specifically, the agency advanced two guiding principles for antimicrobial use in animals: (1) "medically important antibiotics," meaning those with demonstrated human clinical uses,[161] should be restricted to disease treatment uses in animals in response to specific pathogens and not be used for purposes such as growth promotion, and (2) antimicrobials should be used under the supervision of a veterinarian, whether through direct oversight or after consultation.[162] This draft guidance, like Guidance #152, did not provide a legal means of enforcement of these principles, and the FDA again explicitly allowed for consideration of alternative approaches to accomplish its stated goals.[163]

In this document, the FDA outlined differences between animal drugs approved before Guidance #152, which did not have to meet microbiological safety standards, and those approved after the guidance was issued.[164] New Animal Drug Applications (NADAs) submitted since 2003 must incorporate risk assessment for drug safety by analyzing potential harm through selection for antimicrobial resistance, or must use alternative methods to evaluate microbiological safety. This change in the drug approval process, although not legally binding (like Guidance #152), shifted the burden of demonstrating human microbiological safety of new antimicrobials to the drug manufacturer. In contrast, to remove a drug approved before 2003 from the market or to amend its approval, the FDA must raise concerns and provide evidence for risk from antimicrobial resistance to humans for these drugs.[165] Many of these

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159. *See* CTR. FOR VETERINARY MED., *supra* note 37. Comments were solicited through the end of August 2010, and the FDA has stated that it intends to issue a final document. *Id.* at 3. At the time of writing, the final document has yet to be released.

160. *Id.* at 13.

161. *Id.* at 3 n.1.

162. *Id.* at 3.

163. *Id.* at 2.

164. *Id.* at 13-15.

165. Proposal To Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry, Docket No. 00N-1571 (Dep't of Health & Human Servs. Mar. 16, 2004) (initial decision at 5); CTR. FOR VETERINARY MED., *supra* note 37, at 14 ("However, initiating action to withdraw an approved new animal drug application (NADA), in whole or in part, based on the results of a post-approval safety review would require the agency to make the showing required under section 512(e)(1) of the [Food, Drug, and Cosmetic] Act.").

drugs have been on the market for decades,[166] which is longer than the surveillance systems have been in existence. This limits the ability of the FDA to provide data on trends in resistance before and after drug approval, which would hinder any FDA effort to justify a drug's withdrawal.

While the new drug approval process is more rigorous in considering antibiotic resistance explicitly, the dichotomy between recommending higher standards for new drug approval and applying lesser standards for existing drugs may serve as a disincentive to drug manufacturers to develop and market new antimicrobials. The Infectious Diseases Society of America (IDSA), representing clinicians and researchers on the front line of antimicrobial resistance, has campaigned for years to address the dwindling pipeline of new antimicrobial drugs needed to combat human and animal disease from highly drug-resistant pathogens.[167]

Of note, the American Veterinary Medical Association (AVMA) provided comment on the draft guidance, stating that it "is concerned that mandating veterinary oversight of veterinary antimicrobials may not guarantee improved veterinary involvement or a valid veterinarian-client-patient relationship," in part due to the availability of medication over the counter and to the established shortage of food animal veterinarians.[168] The AVMA also speculated that "antimicrobials used for production purposes may have unknown mechanisms of action which may actually be therapeutic," going further to suggest that medically important antimicrobials used for production purposes (i.e., for growth promotion) should be relabeled for therapeutic use instead, avoiding FDA's stated recommendations to limit growth promotion use.[169]

E. Veterinary Feed Directive Drugs

Medicated feeds containing antimicrobial drugs have been used since the 1940s and 1950s,[170] and this use became widespread in the

166. *See* Love et al., *supra* note 78, at 280.

167. *See* Helen W. Boucher et al., *Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America*, 48 CLINICAL INFECTIOUS DISEASES 1 (2009).

168. Letter from W. Ron DeHaven, Exec. Vice President, Am. Veterinary Med. Ass'n, to FDA (Aug. 30, 2010), http://www.avma.org/advocacy/federal/regulatory/public_health/10-08_FDA_Draft_Guidance_209_AVMA_Comments.pdf.

169. *Id.*

170. Use of growth-promoting antibiotics in medicated animal feed was shown to be associated with increased rates of animal weight gain. Love et al., *supra* note 78, at 280 (citing F.T. Jones & S.C. Ricke, *Observations on the History of the Development of Antimicrobials and Their Use in Poultry Feeds*, 82 POULTRY SCI. 613 (2003)). However, the use of antibiotics in feed was coupled with industrialization of the animal production process, in which high-throughput

United States and globally during the 1960s and 1970s.[171] In the United States, the FDA regulates medicated animal feeds, which deliver nonprescription antimicrobials, differently than it regulates pharmaceutical grade antimicrobials typically used for therapeutic indications.[172] New drugs for use in animal feed, including antimicrobials, are divided into two categories on the basis of withdrawal period (i.e., the length of time required between cessation of drug delivery and harvesting of milk or meat from the animal).[173] Category I drugs require no withdrawal period.[174] Category II drugs require a withdrawal period.[175] These categories are each subdivided into Type A, Type B, and Type C medicated feeds, on the basis of manufacturing guidelines.[176] The length of withdrawal typically depends on the amount of a drug that could remain in milk or meat at the time of harvesting, otherwise known as the drug's "residue."[177] Antimicrobial drug residues are considered potentially harmful to human health either through human drug sensitivity (i.e., allergic reaction), promotion of antimicrobial resistance,

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techniques were combined with single-species raising in small spaces (barns or feedlots) and commodity feed supplementation. *See* PEW COMM'N ON INDUS. FARM ANIMAL PROD., *supra* note 28, at 5-7. As a result, disentangling the exact mechanism of action of the antibiotics used for growth promotion has been difficult; scientists and others speculate that bacterial metabolic effects, host microbial ecology effects, and effects from treatment of subclinical disease may play roles independently or in combination. *See* Kiser, *supra* note 107, at 1063. Further, in some settings, use of growth promoting antibiotics has little or no positive effect on animal growth and no economic benefit. *See* Jay P. Graham et al., *Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis*, 122 PUB. HEALTH REP. 79, 79 (2007).

171. Love et al., *supra* note 78, at 280 (citing L.E. Hanson, *Feed Additives: The Rationale for Medicated Feeds*, 11 J. AGRIC. & FOOD CHEMISTRY 365 (1963)).

172. New Animal Drugs for Use in Animal Feeds, 21 C.F.R. pt. 558 (2011).

173. *Id.* § 558.3(b)(1).

174. *Id.* § 558.3(b)(1)(i).

175. *Id.* § 558.3(b)(1)(ii).

176. *Id.* § 558.3. Type A medicated articles are used for manufacture of another Type A medicated article or for production of Type B or Type C medicated feed. *Id.* § 558.3(b)(2). Type B medicated feeds are used for the manufacture of other medicated feeds and contain nutrients (e.g., minerals or vitamins). *Id.* § 558.3(b)(3). Type C medicated feeds are complete feeds (i.e., contain all nutrients needed) or are "top-dressed" feeds (often literally placed on top of other feed). *Id.* § 558.3(b)(4). These are offered as free-choice supplements, meaning that animals choose how much of the medicated feed—and therefore the drug—to consume. *Id.* These contain nutrients (e.g., vitamins and minerals) and other nutritional ingredients, and are produced by diluting Type A medicated articles or Type B medicated feeds. *Id.* Certain licenses are required for manufacturers, or feed mills, of Type B or Type C medicated feeds. *Id.* § 558.4.

177. J.M. Mitchell et al., *Antimicrobial Drug Residues in Milk and Meat: Causes, Concerns, Prevalence, Regulations, Tests, and Test Performance*, 61 J. FOOD PROTECTION 742, 742-43 (1998).

or disruption of normal microflora in the intestinal microbiome[178] of humans who consume the residues inadvertently in food products.[179]

Recent FDA efforts have amended this regulatory structure to provide some veterinary oversight of this otherwise nonprescription process. In 1996, the FDA added a new class of medications for addition to animal feeds, known as "veterinary feed directive" (VFD) drugs;[180] VFD regulations currently are under review.[181] VFD drugs are antimicrobials or other drugs for which the FDA considers the risks too high for over-the-counter marketing.[182] VFD drugs require a written statement by a licensed veterinarian, akin to a prescription written in the context of a valid veterinary-patient-client relationship,[183] which orders the use of the VFD drug in animal feed.[184] Although the AVMA has advocated for a number of changes to the logistic structure of the process, veterinary professional groups, including food animal practitioners, generally have supported the VFD requirements.[185]

F. Fluoroquinolone Ban in Poultry

Fluoroquinolones, as a class of antimicrobials, were introduced to human clinical use in the mid-1980s.[186] In the mid-1990s, these drugs,

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178. Linda Tollefson et al., *Regulation of Antibiotic Use in Animals*, *in* ANTIMICROBIAL THERAPY IN VETERINARY MEDICINE 417, 417, 421 (Steeve Giguère et al. eds., 4th ed. 2006).

179. *See* C.D. Van Houweling & J.H. Gainer, *Public Health Concerns Relative to the Use of Subtherapeutic Levels of Antibiotics in Animal Feeds*, 46 J. ANIMAL SCI. 1413, 1420-21 (1978).

180. 21 C.F.R. § 558.3(b)(6)-(7).

181. Veterinary Feed Directive, 75 Fed. Reg. 15,387 (Mar. 29, 2010) (to be codified at 21 C.F.R. pts. 510, 514, 558).

182. *See* 21 U.S.C. § 354 (2006) (laying out general VFD drug requirements).

183. *Id.* § 354(a)(1). Unlike actual prescriptions, VFD orders circumvent state pharmacy laws while providing for a higher degree of professional control than the typical, over-the-counter labels approved for the majority of medicated animal feeds. *See id.* At the time of writing, this category only had been used for one new antimicrobial, Schering-Plough's Aquaflor®, or florfenicol (a drug related to chloramphenicol), approved in 2005 (NADA 141-246; a Type A medicated feed article used to make Type C medicated feed for catfish). *See infra* Appendix II: Critically-Important Antibiotics. Chloramphenicol is rarely employed for human clinical use due to toxicity concerns. *See* Editorial, *Fatal Aplastic Anemias from Chloramphenicol*, 247 NEW ENG. J. MED. 183 (1952).

184. Animal Drug Availability Act; Veterinary Feed Directive, 65 Fed. Reg. 76,924, 76,924 (Dec. 8, 2000) (to be codified at 21 C.F.R. pts. 510, 514, 558).

185. Letter from W. Ron DeHaven, Exec. Vice President & CEO, Am. Veterinary Med. Ass'n, to FDA (Aug. 26, 2010), http://www.avma.org/advocacy/federal/regulatory/practice_issues/drugs/Veterinary_Feed_Directive_comments.pdf (regarding the American Veterinary Medical Association's support of VFD oversight of over-the-counter antimicrobial drugs for food animal use).

186. Amita Gupta et al., *Antimicrobial Resistance Among* Campylobacter *Strains, United States, 1997-2001*, 10 EMERGING INFECTIOUS DISEASES 1102, 1107 fig.2 (2004).

including enrofloxacin,[187] were approved for use in food-producing animals.[188] Enrofloxacin, as a chemical, is metabolized in animals to the human drug ciprofloxacin.[189] In poultry, enrofloxacin may be administered to a whole flock as a water additive, which may lead to variation in the dose each chicken receives (e.g., a sick chicken may consume less because the animal is not eating well due to illness).[190] Such in-feed or in-water administration, because of the variation in dosing, is known to select for resistance in bacteria that colonize treated chickens.[191]

The NARMS surveillance network recorded no ciprofloxacin resistance among *Campylobacter jejuni*[192] isolates from poultry products in 1989 and 1990, before the approval for use in food-producing animals.[193] After the authorization, scientists found rising trends of resistance to ciprofloxacin in *Campylobacter* strains using data from NARMS.[194] Among humans, eating chicken products was found to be a risk factor for a human having a ciprofloxacin-resistant *Campylobacter*.[195] In addition, particular *Campylobacter* strains causing disease in humans

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187. Baytril®, or enrofloxacin, is a relative of the human drug ciprofloxacin used to treat humans exposed to the bioterrorism agent anthrax. Letter from John B. Payne, Senior Vice President, Bayer Animal Health (Mar. 21, 2002), http://www.uspoultry.org/positionpapers/docs/ppbayer.pdf. Ciprofloxacin also is used to treat humans with other clinically important infections. *See* FDA, *supra* note 89, at 10.

188. S. Zhao et al., *Antimicrobial Resistance of* Campylobacter *Isolates from Retail Meat in the United States Between 2002 and 2007*, 76 APPLIED & ENVTL. MICROBIOLOGY 7949, 7954 (2010); Animal Drugs, Feeds, and Related Products; Enrofloxacin for Poultry; Withdrawal of Approval of New Animal Drug Application, 70 Fed. Reg. 44,048 (Aug. 1, 2005) (to be codified at 21 C.F.R. pts. 520, 556).

189. *See* Poul Nielsen & Nils Gyrd-Hansen, *Bioavailability of Enrofloxacin After Oral Administration to Fed and Fasted Pigs*, 80 PHARMACOLOGY & TOXICOLOGY 246, 246 (1997).

190. Love et al., *supra* note 78, at 280.

191. *See* Luke P. Randall et al., *Modification of Enrofloxacin Treatment Regimens for Poultry Experimentally Infected with* Salmonella enterica *Serovar Typhimurium DT104 To Minimize Selection of Resistance*, 50 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 4030 (2006); Michiel van Boven et al., *Rapid Selection of Quinolone Resistance in* Campylobacter jejuni *but Not in* Escherichia coli *in Individually Housed Broilers*, 52 J. ANTIMICROBIAL CHEMOTHERAPY 719 (2003).

192. *C. jejuni* is a food-borne enteric pathogen that may be found in poultry at high rates (90-100% of birds) without causing signs of disease in the birds. *See* B.A. McCrea et al., *A Longitudinal Study of* Salmonella *and* Campylobacter jejuni *Isolates from Day of Hatch Through Processing by Automated Ribotyping*, 69 J. FOOD PROTECTION 2908, 2908 (2006).

193. Zhao et al., *supra* note 188, at 7949 (citing Gupta et al., *supra* note 186).

194. *Id.*; Gupta et al., *supra* note 186, at 1107 fig.2 (citing Kirk E. Smith et al., *Quinolone-Resistant* Campylobacter Jejuni *Infections in Minnesota, 1992-1998*, 340 NEW ENG. J. MED. 1525 (1999)) (demonstrating trends of rising resistance after approval of fluoroquinolones for use in poultry).

195. Heidi D. Kassenborg et al., *Fluoroquinolone-Resistant* Campylobacter *Infections: Eating Poultry Outside of the Home and Foreign Travel Are Risk Factors*, 38 CLINICAL INFECTIOUS DISEASES S279, S281-82 (Supp. 2004).

were matched to strains found in retail chicken products.[196] Based on this evidence, the FDA proposed restrictions on fluoroquinolones in 2000 by publishing its intent to withdraw approval of the NADA for use of enrofloxacin in poultry.[197]

Both approval and withdrawal of approval can occur through FDA action.[198] Withdrawal of drug approval carries a different regulatory burden than the approval mechanism. Specifically, drug manufacturers must prove efficacy and safety for drug approval, but the FDA, not the drug manufacturer, has the initial burden of raising questions about the safety of drugs already on the market.[199] Once this initial burden of production has been met, the burden of persuasion shifts to the drug manufacturer to prove that the drug indeed remains safe.[200] This "safety clause" allows for review of drugs when new evidence, beyond that provided with the initial application, becomes available.[201] This is in contrast to regulatory efforts in other industries, such as chemical production (similar in that most antimicrobials are chemical compounds), in which the burden of proof at all stages is on the producer to demonstrate safety.[202]

Guidance #78, finalized in 1999, "states that FDA believes it is necessary to consider the potential human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs."[203] This expansion of "safety" to include both direct toxic effects from a chemical, as well as indirect effects on human health from

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196. Smith et al., *supra* note 194, at 1530.

197. Enrofloxacin for Poultry; Opportunity for Hearing, 65 Fed. Reg. 64,954, 64,954-55 (Oct. 31, 2000).

198. *See supra* Part III.D. *See generally* Tollefson et al., *supra* note 178, at 417-23 (discussing drug approval and withdrawal of approval).

199. 21 U.S.C. § 360b(e)(1) & (B) (Supp. 2008); *see* Tollefson et al., *supra* note 178, at 417-23.

200. Briceño, *supra* note 33, at 531 (citing Withdrawal of Approval of New Animal Drug Application for Enrofloxacin in Poultry, Docket No. 2000N-1571, at 8 (Dep't of Health & Human Servs., July 28, 2005) (final decision); Hess & Clark, Div. of Rhodia, Inc. v. FDA, 495 F.2d 975, 992 (D.C. Cir. 1974)). This occurs in the context of a regulatory hearing before a hearing officer under Part 16 of the regulations and can be appealed to the Commissioner. *See id.* at 529.

201. 21 U.S.C. § 360b(e)(1)(B); Tollefson et al., *supra* note 178, at 417, 423.

202. Toxic Substances Control Act, 15 U.S.C. § 2603 (2006).

203. CTR. FOR VETERINARY MED., FDA, HUMAN HEALTH IMPACT OF FLUOROQUINOLONE RESISTANT CAMPYLOBACTER ATTRIBUTED TO THE CONSUMPTION OF CHICKEN, at I-2 (2000), http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/UCM152308.pdf (citing CTR. FOR VETERINARY MED., FDA, DRAFT GUIDANCE FOR THE INDUSTRY: EVALUATION OF THE HUMAN HEALTH IMPACT OF THE MICROBIAL EFFECTS OF ANTIMICROBIAL NEW ANIMAL DRUGS INTENDED FOR USE IN FOOD-PRODUCING ANIMALS (Nov. 1998), http://www.fda.gov/ohrms/dockets/98fr/980969gd.pdf).

antimicrobial resistance, was an important regulatory step that allowed the FDA to justify restriction of fluoroquinolones.[204]

NARMS data informed a risk assessment performed by the FDA in 2000, in which the agency quantified the increased risk to human health from fluoroquinolone use in poultry production.[205] After prolonged administrative litigation with Bayer, the company that produces enrofloxacin,[206] the FDA ultimately succeeded in banning fluoroquinolone use in poultry in 2005.[207] At the time of writing, the fluoroquinolone ban was the only risk assessment-based policy[208] designed to address public health concerns with antimicrobial resistance of agricultural origin in the United States.[209]

IV. RECENTLY PROPOSED LEGISLATION TO ADDRESS ANTIMICROBIAL RESISTANCE

Although the FDA has the authority to regulate the use of antimicrobial drugs based on evidence of antimicrobial resistance, it has not done so in most cases.[210] As a result, numerous stakeholders outside the FDA have advocated for additional laws and regulatory efforts to restrict antimicrobial use in food-producing animals.[211] In May 2011, a group of organizations, led by the Natural Resources Defense Council

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204. *See id.*

205. *Id.* at I-2 to -3.

206. LAXMINARAYAN ET AL., *supra* note 68, at 106.

207. Animal Drugs, Feeds, and Related Products; Enrofloxacin for Poultry; Withdrawal of Approval of New Animal Drug Application, 70 Fed. Reg. 44,048 (Aug. 1, 2005) (codified at 21 C.F.R. pts. 520, 556); Zhao et al., *supra* note 188, at 7954.

208. The uncertainties inherent to any risk assessment, which are particularly profound for microbial risk assessment, were attacked by Bayer, the company that produces Baytril®, during its effort to stop the FDA's withdrawal of approval. *See* Briceño, *supra* note 33, at 531 (citing Withdrawal of Approval of New Animal Drug Application for Enrofloxacin in Poultry, Docket No. 2000N-1571 (Dep't of Health & Human Servs., July 28, 2005) (final decision)). These risk assessment techniques have also been hotly debated in the scientific community. *See* Beth J. Feingold et al., *A Niche for Infectious Disease in Environmental Health: Rethinking the Toxicological Paradigm*, 118 ENVTL. HEALTH PERSP. 1165 (2010); *see also* Simon Toze et al., *Use of Static Quantitative Microbial Risk Assessment To Determine Pathogen Risks in an Unconfined Carbonate Aquifer Used for Managed Aquifer Recharge*, 44 WATER RES. 1038, 1039 (2010).

209. *See Preservation of Antibiotics for Medical Treatment Act (PAMTA): Hearing on H.R. 1549 Before the H. Comm. on Rules*, *supra* note 31, at 22-23, 27 (statement of Margaret Mellon) (noting FDA's failure to use its authority to restrict antibiotic use except in the case of fluoroquinolones in poultry).

210. *Id.*

211. *See* R. Finch & P.A. Hunter, *Antibiotic Resistance—Action To Promote New Technologies: Report of an EU Intergovernmental Conference Held in Birmingham, UK 12-13 December 2005*, 58 J. ANTIMICROBIAL CHEMOTHERAPY i3, i12 (Supp. 2006) (urging for improved international regulation); AM. SOC'Y FOR MICROBIOLOGY, *supra* note 5, at 5-6; MELLON ET AL., *supra* note 17, at 6-7; Bartlett et al., *supra* note 27, at 4.

(NRDC), filed a lawsuit against the FDA, alleging that the "FDA's failure to withdraw approvals for subtherapeutic uses of penicillin and tetracyclines in animal feed constitutes an agency action unlawfully withheld in violation of the Administrative Procedure Act (APA)" and further, that FDA "unreasonably delayed ruling" on petitions submitted by named parties in the lawsuit in 1999 and 2005 regarding these withdrawals.[212] In response to the lawsuit, Representative Louise Slaughter, who introduced the most recent PAMTA bill to the House of Representatives,[213] stated, "The FDA needs to take common sense steps to reduce the needless use of antibiotics in healthy animals, and protect human beings."[214] In late December 2011, however, the FDA published a notice announcing a withdrawal of its original 1977 notice of opportunity for hearing regarding its proposal to restrict certain uses for tetracycline and penicillin antimicrobial drugs in animal feed.[215]

Justification for the need for legislation to ban certain uses of antimicrobials in food animals has been two-fold. Scientific evidence to support the link between antimicrobial use in livestock and antimicrobial resistance in human pathogens has been growing, bolstered in part by enhancement of the NARMS program.[216] An economic argument in favor of reducing antimicrobial resistance also has been made because of the high human cost from illness, death, and treatment of antimicrobial-resistant infections, including those acquired from food sources contaminated by animal waste.[217] The Task Force estimated the health care cost of treating hospital-acquired infections from just six common resistant bacteria at $1.3 billion annually (1992 dollars).[218] Costs of prevention efforts compared to the costs of treating disease are difficult

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212. First Amended Complaint for Declaratory and Injunctive Relief at 3, Natural Res. Def. Council, Inc. et al. v. U.S. Food & Drug Admin. et al., No. 11 CIV 3562 (RMB) (S.D.N.Y. July 7, 2011), *available at* http://docs.nrdc.org/health/files/hea_11052501a.pdf.

213. *See infra* Part IV.B.

214. Press Release, Congresswoman Louise M. Slaughter, Slaughter Says Lawsuit Against FDA Shows Growing Public Awareness, Concern over Antibiotic Overuse (May 25, 2011), http://www.slaughter.house.gov/index.php?option=com_content&view=article&id=2485:slaughter-says-lawsuit-against-fda-shows-growing-public-awareness-concern-over-antibiotic-overuse&catid=95:2011-press-releases&Itemid=55.

215. Withdrawal of Notices of Opportunity for a Hearing; Penicillin and Tetracycline Used in Animal Feed, 76 Fed. Reg. 79,697 (Dec. 22, 2011).

216. *See supra* Part III.A.

217. *See* Preservation of Essential Antibiotics for Human Diseases Act of 1999, H.R. 3266, 106th Cong. § 2 (1999).

218. Interagency Task Force on Antimicrobial Resistance, *supra* note 130, at 10 (citing OFFICE OF TECH. ASSESSMENT, U.S. CONG., OTA-H-629, IMPACTS OF ANTIBIOTIC RESISTANT BACTERIA (1995)).

to estimate,[219] but some studies show that preventing disease may be cost effective.[220] Regardless, preventing human (and animal) suffering and death from antimicrobial-resistant infections is of incalculable benefit.

A. Strategies To Address Antimicrobial Resistance Act

Although the Task Force has continued to meet, official appropriations to fund it expired in 2006.[221] The Strategies To Address Antimicrobial Resistance (STAAR) Act would amend the Public Health Service Act to create an Office of Antimicrobial Resistance (OAR) within HHS modeled on the Task Force.[222] The bill was first introduced into the House by Representative Jim Matheson (D-UT) in September 2007[223] and into the Senate by Senator Sherrod Brown (D-OH) in November 2007.[224] The STAAR bill did not emerge from committee during either the 110th Congress or the 111th Congress, and, at the time of writing, had not been reintroduced to the 112th Congress.[225]

The IDSA, Society for Healthcare Epidemiology of America (SHEA), American Medical Association (AMA), American Public Health Association (APHA), and related professional organizations touted the potential ability of the STAAR act to help improve "U.S. coordination and specific actions designed to better monitor, treat, and most importantly prevent the development and transmission of drug resistant microbes that threaten the health of all Americans."[226] The major strength of the STAAR Act would be to provide a centralized office, the OAR, to help coordinate the multiagency response to the threat of

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219. Coast & Smith, *supra* note 7, at 241; John E. McGowan, Jr., *Economic Impact of Antimicrobial Resistance*, 7 EMERGING INFECTIOUS DISEASES 286, 290-91 (2001) (concerning, not just difficulties in estimating cost-benefit on a societal level, but also the need for improved national laboratory surveillance to do so).

220. *See, e.g.*, R.E. Nelson et al., *Cost-Effectiveness of Adding Decolonization to a Surveillance Strategy of Screening and Isolation for Methicillin-Resistant* Staphylococcus Aureus *Carriers*, 16 CLINICAL MICROBIOLOGY & INFECTION 1740, 1745 (2010) (a single-pathogen, single-hospital intervention).

221. Strategies To Address Antimicrobial Resistance Act, H.R. 3697, 110th Cong. § 2(11) (2007).

222. *Id.* § 3(a)(1).

223. *Id.* at 1.

224. Strategies To Address Antimicrobial Resistance Act, S. 2313, 110th Cong., at 1 (2007).

225. *See Search Bill Summary & Status*, LIBRARY CONGRESS, http://thomas.loc.gov/home/LegislativeData.php?&n=B55&C=110 (search "strategies to address antimicrobial resistance") (last visited Mar. 23, 2012).

226. Letter from the STAAR Act Coalition to Representative Nancy Pelosi, Speaker, U.S. House of Representatives (May 18, 2009), http://www.ada.org/sections/advocacy/pdfs/ltr_090514_hr2400_staar.pdf.

antimicrobial resistance.[227] How this new office would choose to implement policy and support research and surveillance would be critical to its success if the STAAR Act is reintroduced and passed into law. Any such national office must have the legal authority to regulate antimicrobial uses, well beyond the nonbinding recommendations the FDA has provided under current law. While coordination of interagency efforts might be enhanced by establishment of a national office, legal and regulatory questions regarding agency jurisdiction would need to be addressed for such an office to succeed.

B. Preservation of Antibiotics for Medical Treatment Act

The Preservation of Antibiotics for Medical Treatment Act (PAMTA) originally was introduced by Representative Brown (D-OH) to the 106th Congress in 1999,[228] and most recently was introduced to the House of Representatives by Representative Slaughter (D-NY),[229] a microbiologist,[230] and to the Senate by Senator Diane Feinstein (D-CA) in 2011 during the 112th Congress.[231] The current PAMTA bill proposes to amend Sections 201[232] and 512[233] of the Federal Food, Drug, and Cosmetic Act,[234] to rescind approval for certain critically important antimicrobials for nontherapeutic use in animals.[235] Specifically, this proposed legislation would require the FDA, within two years, to eliminate the nontherapeutic use of eight classes of antimicrobials in food-producing animals, subject to certain exceptions.[236] The bill was introduced in response to the government's failure to address the *Action*

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227. *See* H.R. 3697 § 3.

228. An earlier version, H.R. 3266, was introduced in 1999 under another name, the "Preservation of Essential Antibiotics for Human Diseases Act of 1999." H.R. 3266, 106th Cong. (1999).

229. Preservation of Antibiotics for Medical Treatment Act of 2011, H.R. 965, 112th Cong. (2011).

230. *Biography*, CONGRESSWOMAN LOUISE M. SLAUGHTER, http://www.louise.house.gov/index.php?option=com_content&view=article&id=39&Itemid=61 (last visited Mar. 23, 2012).

231. Preservation of Antibiotics for Medical Treatment Act of 2011, S. 1211, 112th Cong. (2011).

232. *See* 21 U.S.C. § 321 (2006).

233. *See id.* § 360b.

234. *See id.* §§ 301-399.

235. *See infra* Appendix II: Critically Important Antibiotics (comparing PAMTA's "medically important antibiotics," with the WHO's "critically important antimicrobials," and human or veterinary uses of the drugs).

236. Preservation of Antibiotics for Medical Treatment Act of 2011, H.R. 965, 112th Cong. § 4(q)(2) (2011). An exception arises if a product is proven not to promote development of antibiotic resistance. *Id.*

Plan's recommendations and the ongoing threats presented by antimicrobial use in agriculture.[237]

In a hearing before the House Committee on Rules, Joshua Sharfstein, representing the FDA, testified that his agency supports PAMTA and restriction on growth promotion uses of antimicrobials in food-producing animals, so long as agricultural uses of antimicrobials for treatment and prevention of disease remain viable alternatives.[238] He suggested that, with PAMTA, the FDA would have additional authority to make timely changes to the approvals of the antimicrobials in question.[239] Subsequent to this Congressional hearing on antimicrobial resistance, the FDA published Draft Guidance #209[240] clarifying its opinion on the issue of nontherapeutic use of antimicrobials in livestock.[241]

Many other key stakeholders, including professional organizations such as the APHA and the AMA, support PAMTA.[242] Of note, the veterinary professional community is not united. Dr. Michael Blackwell, a veterinarian and vice-chairman of the Pew Commission on Industrial Farm Animal Production, commented, "The veterinary community has been conspicuously absent from the critical effort to rein in non-therapeutic antibiotic uses."[243] While the Humane Society Veterinary Medical Association (HSVMA) has expressed support for PAMTA,[244] the American Veterinary Medical Association (AVMA) has opposed the bill and actively advocated for its defeat.[245] Some have argued that the

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237. H.R. 965 § 2.

238. *Preservation of Antibiotics for Medical Treatment Act (PAMTA): Hearing on H.R. 1549 Before the H. Comm. on Rules*, *supra* note 31, at 13-14 (statement of Joshua M. Sharfstein on the 2009 version of PAMTA).

239. *Id.* at 14.

240. *See* discussion *supra* Part III.D.

241. CTR. FOR VETERINARY MED., *supra* note 37, at 3.

242. Preservation of Antibiotics for Medical Treatment Act of 2011, S. 1211, 112th Cong. § 2(16) (2011).

243. *HSVMA Launches Veterinary Petition Targeting Antibiotic Overuse*, HUMANE SOC'Y VETERINARY MED. ASS'N 1 (Jan. 12, 2011), http://www.hsvma.org/index.php?view=article&catid=20%3Aadvocay&id=84%3Aantibiotic_overuse_petition_011211.html+&format=pdf&option=com_content&Itemid=1.

244. *Id.*

245. *S. 619/H.R. 1549: Preservation of Antibiotics for Medical Treatment Act of 2009*, AM. VETERINARY MED. ASS'N, http://www.avma.org/advocacy/federal/legislative/111th/issue_briefs/preservation_of_antibiotics_act_of_2009_issue_brief.pdf (last visited Mar. 23, 2012); R. Scott Nolen, *AVMA Cautions Against Indiscriminate Broad Bans on Livestock Antimicrobials: Unsafe Food Supply Could Threaten Public Health*, AM. VETERINARY MED. ASS'N (Aug. 1, 2008), http://www.avma.org/onlnews/javma/aug08/080801a.asp.

AVMA's position on the PAMTA bill remains one of the strongest barriers to its passage.[246]

The AVMA's position statements on this issue cited evidence that was inconsistent with scientific literature and testimony published at the time. For example, the AVMA's position statement on the 2009 PAMTA bill asserted:

> Denmark, with a pork industry roughly equivalent to the size of the pork herd in Iowa, instituted a ban on the use of antibiotics as growth promoters (AGPs) in 2000 which has *not* reduced antibiotic resistance patterns in humans. The ban has, however, resulted in increased death and disease among animals, greater amounts of antibiotics used to treat and prevent disease, and little evidence to suggest that antibiotic resistance in humans has declined.[247]

Contrasting this statement, Danish researchers, some of whom represent their national food safety agencies, have produced multiple reports, published peer-reviewed scientific articles, and offered testimony to the U.S. Congress about: (1) the reduction in antimicrobial resistance in humans following the ban for multiple antimicrobials previously used for growth promotion, and (2) brief increases in animal mortality that did not detract from overall trends of increasing swine production.[248] In her call for a global effort to combat antimicrobial resistance in honor of World Health Day 2011, Dr. Margaret Chan noted that "veterinarians in some countries earn at least 40% of their income from the sale of drugs,

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246. Ashley Colpaart, *PAMTA—Antibotic* [*sic*] *Resistance and Animal Agriculture*, FRIEDMAN SPROUT (Mar. 1, 2010, 2:42 AM), http://friedmansprout.com/2010/03/01/pamta-antibotic-resistance-and-animal-agriculture/.

247. *S. 619/ H.R. 1549: Preservation of Antibiotics for Medical Treatment Act of 2009*, *supra* note 245.

248. Letter from Frank M. Aarestrup, Professor, Danish Technical Univ., to Representative Nancy Pelosi, Speaker, U.S. House of Representatives (Sept. 19, 2009), http://www.louise.house.gov/images/stories/attachments/2009.10.01.pamta.pdf ("[V]arious rumours and sometimes 'creative' interpretations of what has taken place in Denmark have been circulated to members of the US Congress, and we are grateful for having been given this opportunity to correct some of these stories."); DANISH INTEGRATED ANTIMICROBIAL RESISTANCE MONITORING & RESEARCH PROGRAMME, DANMAP 2007—USE OF ANTIMICROBIAL AGENTS AND OCCURRENCE OF ANTIMICROBIAL RESISTANCE IN BACTERIA FROM FOOD ANIMALS, FOODS AND HUMANS IN DENMARK 14-16 (2008), http://www.danmap.org/Downloads/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2007.ashx; Anette M. Hammerum et al., *Comment on: Withdrawal of Growth-Promoting Antibiotics in Europe and Its Effects in Relation to Human Health*, 30 INT'L J. ANTIMICROBIAL AGENTS 466, 466 (2007); Aarestrup et al., *supra* note 23, at 2056-58; A.E. van den Bogaard et al., Correspondence, *The Effect of Banning Avoparcin on VRE Carriage in the Netherlands*, 46 J. ANTIMICROBIAL CHEMOTHERAPY 146, 146 (2000); Emborg & Wegener, *supra* note 24, at 168-69; *see infra* Part V.B.

creating a strong disincentive to limit their use."[249] Whether economic incentives might influence the AVMA's position on PAMTA is unclear.[250]

For agribusiness, the economic incentives have been a keystone of its opposition of PAMTA. The National Pork Board has touted an Iowa State University Extension study that claimed the cost of a ban on nontherapeutic uses of antimicrobials would exceed $700 million to the U.S. pork industry and that the cost, passed along to consumers, would lead to a 2% increase in the price of pork products.[251] The sheer distribution volume (over 13 million kg)[252] for antimicrobials intended for use in food-producing animals in the United States underscores the economic importance of this use for manufacturers of the drugs. The National Research Council's Board on Agriculture estimated that, for pharmaceutical companies, the animal health industry produced $3.3 billion in sales compared to human health drug sales of $63 billion during 1995.[253]

Although agribusiness assessments for cost and quantity of antimicrobial use often are not disclosed to the public, Graham and colleagues used data from the Perdue company to find that, while nontherapeutic doses of antibiotics did offset poor husbandry and improved gains, the production benefit failed to outweigh the antibiotic cost, resulting in a net loss of $0.0093 per chicken.[254] Another study in dairy calves found a $10-per-calf economic benefit from using a targeted

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249. *World Health Day 2011: Director-General Statement*, *supra* note 1, at 2.

250. U.S. veterinarians typically earn 30% or more of their gross practice income from drug sales. *See* Karen Felsted, *Veterinary Produce Sales Are Changing? Get On Board*, DVM360.COM (Sept. 1, 2010), http://veterinarybusiness.dvm360.com/vetec/article/articleDetail.jsp?id=685795. In contrast, in Sweden, veterinarians are allowed only to prescribe and not sell drugs. Claire B. Andreasen et al., *Swedish Antimicrobial Regulations and Their Impact on Food Animal Production*, 227 J. AM. VETERINARY MED. ASS'N 41, 41 (2005) (citing C. Greko, *Use of Antibiotics for Animals from 1980-1997*, *in* PROCEEDINGS 8 (1998)). Of interest, Sweden was the first country in the European Union to ban antimicrobial growth promoters in food-producing animals. *See infra* Part V.B. This ban was established voluntarily by farmers in the early 1980s (preceding the official government ban) to prevent certain farmers from having an economic advantage over others through use of the drugs. *See* Andreasen et al., *supra*, at 41.

251. Dermot J. Hayes & Helen H. Jensen, *Implications of More Restricted Antimicrobial Access Policy: Issues Related to U.S. Pork Production*, *in* 2 PERSPECTIVES IN WORLD FOOD AND AGRICULTURE, *supra* note 24, at 175, 178; *The Danish Experience: What Happened When Denmark Banned the Subtherapeutic Use of Antibiotic Growth Promotants?*, PORK CHECKOFF, http://www.pork.org/filelibrary/Factsheets/DanishExperience.pdf (last visited Mar. 23, 2012) (citing DERMOT HAYES ET AL., NAT'L PORK BD., ANALYSIS OF A MORE RESTRICTED ANTIMICROBIAL ACCESS POLICY IN PORK PRODUCTION-NPB #02-104, http://www.pork.org/FileLibrary/Research Documents/02-104-HAYES-ISU.pdf (last visited Mar. 23, 2012)).

252. CTR. FOR VETERINARY MED., *supra* note 18, at iv tbl.1.

253. COMM. ON DRUG USE IN FOOD ANIMALS ET AL., THE USE OF DRUGS IN FOOD ANIMALS: BENEFITS AND RISKS 180-81 (1999).

254. Graham et al., *supra* note 170, at 79.

(i.e., veterinary-directed) treatment only when calves were ill rather than using more widespread treatment.[255] In this clinical trial, randomized groups of dairy calves were given either conventional treatment for any symptoms of diarrhea or targeted treatment of diarrhea only when the calf had a fever or other clinical signs of illness (i.e., based on veterinary recommendation to treat).[256] Further, the study found that feeding antimicrobials in the milk actually led to more days of diarrhea and did not improve the weight gain of the calves.[257] Well-designed studies like this one[258] support the potential economic and veterinary clinical feasibility of implementing regulation to remove nontherapeutic uses of antimicrobials. Further evidence for both minimal economic impacts to industry and benefits to public health comes from examination of the effects of regulation in the European Union.

V. THE EUROPEAN REGULATORY EXPERIENCE

The existence of international programs to standardize regulatory processes for veterinary drugs[259] makes consideration of global policy germane to a discussion of veterinary drug regulation in the United States. In 1996, the World Organisation for Animal Health (OIE)[260] established an international body, the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), to synchronize the registration standards for veterinary products and surveillance standards for post-marketing evaluation of approved veterinary drugs internationally.[261] Both the United States and the European Union have adopted many VICH

255. A.C.B. Berge et al., *Targeting Therapy To Minimize Antimicrobial Use in Preweaned Calves: Effects on Health, Growth, and Treatment Costs*, 92 J. DAIRY SCI. 4707, 4713 (2009).

256. *Id.* at 4708-09.

257. *Id.* at 4711-12.

258. Randomized clinical trials (also referred to as randomized controlled trials or RCTs) are the scientific gold standard for interventional research. *See* LEON GORDIS, EPIDEMIOLOGY 115 (3d ed. 2004).

259. *See* Tollefson et al., *supra* note 178, at 417-18.

260. At the time, the World Organisation for Animal Health was called the Office International des Epizooties (OIE). The OIE is a global reference body, headquartered in Paris with 178 member countries, dedicated to international cooperation to combat animal diseases. *About Us*, WORLD ORG. FOR ANIMAL HEALTH, http://www.oie.int/about-us/ (last visited Mar. 23, 2012). The United States is a member of this 80-year-old world organization. *The 178 OIE Members*, WORLD ORG. FOR ANIMAL HEALTH, http://www.oie.int/about-us/our-members/member-countries/ (last visited Mar. 23, 2012).

261. Tollefson et al., *supra* note 178, at 417.

standards.[262] Further, the United States has acknowledged the importance of global efforts to combat antimicrobial resistance.[263]

Despite this attempt at harmonization, European Union members and other countries have progressed ahead of the United States in regulatory and surveillance efforts for nontherapeutic uses of antimicrobials in livestock.[264] Therefore, evaluating the success of European regulation may provide useful insights for efforts in the United States, particularly because European countries and the United States have comparable levels of economic development and employ similar methods of agricultural production.[265] What follows is not meant to be an exhaustive review, but to illustrate historical and current efforts, noting joint programs with the United States where appropriate, that may inform consideration of U.S. regulation of antimicrobial resistance.[266]

A. History of European Regulation

The history of policies to address antimicrobial resistance of agricultural origin began in England.[267] In 1960, the Netherthorpe Committee was established[268] to consider whether feeding antimicrobials to food-producing animals was potentially hazardous to human or animal health.[269] Although the Netherthorpe Committee did not find evidence of risk from such practices, later scientific evidence regarding the development of multiple drug resistance from animal feeding of antimicrobials re-opened the issue.[270] A new committee, dubbed the Swann Committee, was formed in 1968, leading to the first European report on the topic.[271] Commissioned by the English Parliament and delivered to the House of Lords in 1969, the Swann Report[272] warned against using the same classes of antimicrobials for growth promotion in

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262. *See id.* at 417-18.

263. INTERAGENCY TASK FORCE ON ANTIMICROBIAL RESISTANCE, *supra* note 132, at 15.

264. *See* Centner, *supra* note 33, at 30-32.

265. *See* P.N. Wilson & A.B. Lawrence, *Animal Husbandry: The Period 1973-1995*, 310 PHIL. TRANSACTIONS ROYAL SOC'Y LONDON B 275 (1985).

266. *See infra* Appendix I: Regulatory Timeline.

267. *See* Kiser, *supra* note 107, at 1058.

268. England's Netherthorpe Committee was established in response to a 1955 meeting of the Agricultural Research Institute of the National Academy of Sciences (NAS) held in Washington, D.C., in which, although resistance in animal microbes to in-feed antimicrobials was found, a conclusion of no hazard to human health was made. *Id.*

269. *Id.*

270. *Id.* at 1058-59.

271. *Id.* at 1060.

272. *Use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann Report)*, 791 PARL. DEB., H.C. (5th ser.) (1969) 1525 (U.K.), *available at* http://hansard.millbanksystems.com/commons/1969/nov/20/use-of-antibiotics-in-animal-husbandry.

animals that were used in human therapy.[273] Although this report recommended the formal establishment of a committee to oversee regulation on the subject, this did not materialize in Britain until 1998.[274] Subsequent efforts in Britain have included the development of a chapter of the Alliance for the Prudent Use of Antibiotics[275] and participation in the international Reservoirs of Antibiotic Resistance (ROAR) network.[276] The ROAR network of scientists, which includes federally funded U.S. researchers, has focused attention on the environmental spread of resistant bacteria and the ecology of pathogenic and nonpathogenic (commensal) organisms in regard to the transfer of resistance genes.[277]

B. European Bans on Antimicrobial Use

Avoparcin, an antimicrobial drug related to the critically important human drug vancomycin, was introduced for use as a growth-promoting antimicrobial (GPA) in food animal production during the 1970s in Europe.[278] Such use rapidly led to the emergence of a large community reservoir of vancomycin-resistant *Enterococcus* (VRE) in both animal and human populations.[279] Further, VRE strains were found in food-producing animals only in countries in which avoparcin was used in animal feed,[280] and not in Sweden or the United States, where avoparcin was not used.[281]

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273. Lord Soulsby, *Antimicrobials and Animal Health: A Fascinating Nexus*, 60 J. ANTIMICROBIAL CHEMOTHERAPY i77, i77 (Supp. 2007).

274. *Id.* (citing SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY, RESISTANCE TO ANTIBIOTICS AND OTHER ANTIMICROBIAL AGENTS, 1997-8, H.L. 7th Report (U.K.), *available at* http://www.publications.parliament.uk/pa/ld199798/ldselect/ldsctech/081vii/st0701.htm).

275. *Id.* at i78 (concerning U.K. involvement). The Alliance for the Prudent Use of Antibiotics (APUA) is an international advocacy organization based at Tufts University in the United States and sponsors the Reservoirs of Antibiotic Resistance network of scientists. *The APUA Global Mission*, ALLIANCE FOR PRUDENT USE ANTIBIOTICS, http://www.tufts.edu/med/apua/about_us/what_we_do.shtml (last visited Mar. 23, 2012).

276. Soulsby, *supra* note 273, at i78.

277. *Project Description*, RESERVOIRS ANTIBIOTIC RESISTANCE NETWORK, http://www.roarproject.org/ROAR/html/about.htm (last visited Feb. 21, 2012) (describing research activities and U.S. funding mechanisms); Soulsby, *supra* note 273, at i78.

278. *See* Wolfgang Witte, *Selective Pressure by Antibiotic Use in Livestock*, 16 INT'L J. ANTIMICROBIAL AGENTS S19, S19, S20 tbl.1 (Supp. 2000).

279. *See id.*; Marc J.M. Bonten et al., *Vancomycin-Resistant Enterococci: Why Are They Here, and Where Do They Come From?*, 1 LANCET INFECTIOUS DISEASES 314, 314 (2001); Silbergeld et al., *supra* note 68, at 1394 (citing Bonten et al., *supra*); F.M. Aarestrup et al., *Associations Between the Use of Antimicrobial Agents for Growth Promotion and the Occurrence of Resistance Among* Enterococcus faecium *from Broilers and Pigs in Denmark, Finland, and Norway*, 6 MICROBIAL DRUG RESISTANCE 63, 65 (2000) (citations omitted); *see also* Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248.

280. The countries are Belgium, Denmark, Finland, France, Germany, Great Britain, the Netherlands, and Norway. Henrik C. Wegener et al., *Use of Antimicrobial Growth Promoters in*

Virginiamycin was introduced to Europe during the same period as avoparcin, but unlike avoparcin, it was used in the United States as well.[282] Not only did resistance to this antimicrobial emerge in animals that were fed the growth promoter,[283] but resistance was found in human clinical isolates *prior* to the release of Synercid,[284] a human drug in the same class as virginiamycin.[285] This initial finding, combined with later molecular evidence,[286] strongly suggested that use of virginiamycin in food-producing animals contributed to human disease. This conclusion was further supported by how rarely human physicians prescribed streptogramin antimicrobial drugs before and after Synercid's release.[287]

In Denmark, avoparcin use in livestock for growth promotion was banned in 1994, and virginiamycin use was banned in 1997.[288] Danish food safety authorities considered the ban a public health success.[289]

Food Animals and Enterococcus faecium *Resistance to Therapeutic Antimicrobial Drugs in Europe*, 5 EMERGING INFECTIOUS DISEASES 329, 331 tbl.1 (1999).

281. *Id.* Sweden banned all growth promoters in 1986, and avoparcin was not approved as a growth promoter in the United States due to concerns about carcinogenicity. *Id.* at 330 (citing L. Clifford McDonald et al., *Vancomycin-Resistant Enterococci Outside the Health-Care Setting: Prevalence, Sources, and Public Health Implications*, 3 EMERGING INFECTIOUS DISEASES 311 (1997)).

282. Witte, *supra* note 278, at S21-22 (citing DANISH INTEGRATED ANTIMICROBIAL RESISTANCE MONITORING & RESEARCH PROGRAMME, DANMAP 98—CONSUMPTION OF ANTIMICROBIAL AGENTS AND OCCURRENCE OF ANTIMICROBIAL RESISTANCE IN BACTERIA FROM FOOD ANIMALS, FOOD AND HUMANS IN DENMARK (1998)).

283. *Id.* at S22 (citations omitted); Aarestrup et al., *supra* note 279, at 68-69.

284. Synercid, also known as quinupristin/dalfopristin (Q/D), was the first streptogramin drug widely released for human use, but its final approval in 1999 came decades after use of virginiamycin began in food-producing animals. *See* Barbara Pavan, *Synercid Aventis*, 1 CURRENT OPINION INVESTIGATIONAL DRUGS 173, 173 (2000). Q/D remains a drug of last resort for certain highly resistant infections, in part due to side effects. *See* Tobias Welte & Mathias W. Pletz, *Antimicrobial Treatment of Nosocomial Meticillin-Resistant* Staphylococcus Aureus *(MRSA) Pneumonia: Current and Future Options*, 36 INT'L J. ANTIMICROBIAL AGENTS 391, 393 tbl.2, 395 (2010).

285. *See* G. Werner et al., *Association Between Quinupristin/Dalfopristin Resistance in Glycopeptide-Resistant* Enterococcus Faecium *and the Use of Additives in Animal Feed*, 17 EUR. J. CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES 401 (1998).

286. *See* Guido Werner et al., *Molecular Analysis of Streptogramin Resistance in Enterococci*, 292 INT'L J. MED. MICROBIOLOGY 81 (2002).

287. The multitude of potential sources of antimicrobial use in both veterinary and human clinical environments for other drugs makes assessment of cause more difficult. *See infra* Part VI.B. In the case of virginiamycin, human uses of related streptogramins did not significantly contribute to antimicrobial pollution for that class of drugs, making this an unusual case and one scientifically useful to consider.

288. Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248, at 2; *see* Centner, *supra* note 33, at 8-16.

289. *See* Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248; *Preservation of Antibiotics for Medical Treatment Act (PAMTA): Hearing on H.R. 1549 Before the H. Comm. on Rules*, *supra* note 31, at 121 (statement of Frank Møller Aarestrup & Henrik Wegener, National Food Institute, Technical University of Denmark).

Overall use of antimicrobials[290] in livestock decreased by over 50%, although therapeutic use did increase slightly.[291] Prevalence of antimicrobial resistance in animal isolates dropped quickly.[292] At the same time, the ban had little negative economic or animal welfare effect on the Danish pig industry.[293] Despite a brief, 1% increase in the mortality of weaner pigs[294] following bans of nontherapeutic use of antimicrobials in this production group, the overall rate of swine production in Denmark has continued to increase.[295] Management changes on Danish farms also may have contributed to the improvements in pig weaner mortality,[296] similar to results found in Sweden following its GPA ban.[297] The Danish chicken industry experienced improvements in production.[298] In broiler chickens, feed-conversion efficiency[299] increased following the ban, and the percent of mortalities decreased.[300]

Based in part on the bans in Denmark and Sweden,[301] the European Union first imposed an EU-wide GPA ban[302] in 1997, withdrawing

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290. This is determined according to milligrams of antibiotic used per kilogram of meat produced.

291. Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248, at 2.

292. *Id.* at 5-7.

293. *Id.* at 1.

294. In industrial animal production, animals often are sectioned into age groups, sometimes called production stages, because these animals will need to be fed differently according to weight and age. "Weaner" pigs are piglets that recently have been moved away from their mothers and a milk diet and onto other foods. Conventionally, this is done at three to five weeks of age. This process is stressful and weaner pigs, like many young food animals, are more susceptible than other age groups to diseases to which they might be exposed. PEW COMM'N ON INDUS. FARM ANIMAL PROD., *supra* note 28, at 86.

295. Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248, at 1-2; *see* Emborg & Wegener, *supra* note 24, at 169; Aarestrup et al., *supra* note 23, at 2056 & tbl.2.

296. Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248, at ii.

297. *See* Andreasen et al., *supra* note 250, at 42.

298. Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248, at ii.

299. Feed conversion is a measure of how much weight an animal gains as a function of the amount of feed it consumes. With efficient feed conversion, most of the feed consumed is used for weight gain. With poor feed conversion, feed (energy) may be used for other purposes (e.g., activity). An analogy is the difference between a human who has a sedentary lifestyle and gains weight rapidly and a human who is very active and, despite having a similar caloric intake, does not gain weight rapidly.

300. Letter from Frank M. Aarestrup to Representative Nancy Pelosi, *supra* note 248, at ii.

301. *See* Andreasen et al., *supra* note 250, at 41-42 (discussing bans in Sweden); J.I.R. Castanon, *History of the Use of Antibiotic as Growth Promoters in European Poultry Feeds*, 86 POULTRY SCI. 2466, 2469-70 (2007) (concerning the legal grounds for permitting antimicrobials in animal feeds in the European Union, particularly the harmonization of restrictions in certain member countries established before accession into European Union membership).

302. These regulatory efforts have not gone unchallenged. Both Alpharma and Pfizer, major pharmaceutical companies that make and market drugs for nontherapeutic use in livestock in the United States and Europe, attempted to overturn the European bans on the basis of (1) alleged errors of risk assessment relating to the scientific evidence, and (2) alleged

approval for the antimicrobial drug avoparcin.[303] In 1998, it withdrew GPA approval for four additional antimicrobials,[304] including virginiamycin.[305] In the same year, the United Kingdom's Parliament updated the 1969 Swann Report to recommend further limits on nontherapeutic use of antimicrobials in food-producing animals and to establish the "Swann Committee."[306] In 2001, the World Health Organization recommended international bans or global management strategies on use of certain classes of antimicrobials for growth promotion where it concludes that use in food-producing animals selects for resistance to antimicrobials of importance to human medicine.[307] Finally, in 2006, the EU banned the four remaining antimicrobials used in growth promotion.[308]

Shortly after the EU-wide bans, decreases in streptogramin (quinupristin-dalfopristin) and glycopeptide (vancomycin) resistance in bacteria isolated from both humans and animals were found across Europe.[309] The strength of surveillance systems within and among European countries made such analyses possible.

C. European Surveillance Programs

Many European countries have developed national surveillance systems for testing foodborne and other bacterial agents, and the efforts

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misapplication of powers, in this case: the application of the precautionary principle, which allows for regulation to proceed when evidence exists for harm but data are incomplete. Case T-70/99, Alpharma, Inc. v. Council, 2002 E.C.R. II-03495, -3546; Case T-13/99, Pfizer Animal Health SA v. Council, 2002 E.C.R. II-3305, -3365. European courts dismissed the cases brought by Alpharma and Pfizer on the grounds that the European Commission, in mandating the original and amended legislation concerning restrictions on feed additives, had proper authorization to do so pursuant to its directive for the protection of animal or human health or the environment. *Alpharma*, 2002 E.C.R. at II-3619; *Pfizer*, 2002 E.C.R. at II-3480; *see* Council Directive 70/524, 1970 O.J. (L 270) 1 (EC) (directive concerning feed additives).

303. Commission Directive 97/6, 1997 O.J. (L 35) 11, 13 (EC).

304. The antimicrobials were: spiramycin, tylosin, bacitracin zinc, and virginiamycin. Soulsby, *supra* note 273, at i77.

305. Council Regulation 2821/98, 1998 O.J. (L 351) 4, 7 (EC).

306. Centner, *supra* note 33, at 3 (citing SELECT COMMITTEE ON SCIENCE AND TECHNOLOGY, *supra* note 274, ch. 3); Soulsby, *supra* note 273, at i77; *see supra* Part V.A.

307. WHO, WHO GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE 1-2 (2001), http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf; *see* Peter Collignon et al., *World Health Organization Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies for the Use of Antimicrobials in Food Production Animals*, 49 CLINICAL INFECTIOUS DISEASES 132, 132 (2009).

308. The antimicrobials were: monensin, avilamycin, salinomycin, and flavomycin. Soulsby, *supra* note 273, at i77-78.

309. Werner et al., *supra* note 286, at 90 (citations omitted); Van den Bogaard et al., *supra* note 248, at 146.

of these agencies are in the process of being harmonized.[310] Although many aspects of these programs are similar to the United States NARMS program and related surveillance networks,[311] a few scientifically appealing characteristics distinguish European systems. In Denmark, development of the DANMAP surveillance program integrated bacterial and antimicrobial surveillance data with detailed surveys of antimicrobial use and geocoded[312] information on farm locations and human and animal cases of disease.[313] Collecting addresses, GPS points, or other geocoded information allows integration of surveillance systems for human and animal pathogens through a spatial matrix, allowing better linkage of outbreaks that occur in temporal and spatial proximity. When funding for expensive molecular testing of isolates is limited, selection of candidate isolates to test may be guided by this kind of epidemiologic evidence. Sweden's Strategic Program for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) combined surveillance across human and veterinary clinical testing (including companion animals) with education both on resistance trends and also judicious use practices.[314]

Efforts at coordination across countries within the European Union may provide a useful model for international efforts for resistance surveillance involving the United States. EU countries and the United States participate in the international SENTRY surveillance program, but this surveillance network focuses exclusively on human clinical isolates.[315] The European Food Safety Authority (EFSA), established in 2002 as part of Europe's food safety program,[316] and the European Centre for Disease Prevention and Control (ECDC), founded in 2005 to coordinate European health agencies,[317] manage a European-wide

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310. *See* Dominique L. Monnet, *Toward Multinational Antimicrobial Resistance Surveillance Systems in Europe*, 15 INT'L J. ANTIMICROBIAL AGENTS 91, 94-95 (2000).

311. *See supra* Part III.A.

312. Geocoding is a technique for converting an address into a point on a map on the basis of latitude and longitude. Researchers can use this information to conduct spatial data analysis comparing sources of antimicrobial contamination with patterns of resistance in human, animal, and environmental bacteria.

313. DANISH INTEGRATED ANTIMICROBIAL RESISTANCE MONITORING & RESEARCH PROGRAMME, *supra* note 248.

314. Andreasen et al., *supra* note 250, at 41-42.

315. *See Surveillance*, JMI LABORATORIES, http://www.jmilabs.com/surveillance/ (last visited Mar. 23, 2012).

316. *About EFSA*, EURO. FOOD SAFETY AUTHORITY, http://www.efsa.europa.eu/en/aboutefsa.htm (last visited Mar. 23, 2012).

317. *Mission*, EURO. CTR. DISEASE PREVENTION & CONTROL, http://www.ecdc.europa.eu/en/aboutus/Mission/Pages/Mission.aspx (last visited Mar. 23, 2012).

program for surveillance of zoonoses and foodborne bacteria.[318] Multinational studies on antimicrobial resistance trends have been conducted since 1999 by the European Antimicrobial Susceptibility Surveillance in Animals (EASSA) program through the European Animal Health Study Centre (CEESA).[319] These studies have demonstrated general trends of decreasing resistance in bacteria isolated from animals following the ban, but also found a few paradoxic plateaus or increases in resistance.[320] Numerous scientists and stakeholders have noted the importance of pre- and postregulation monitoring.[321]

Collectively, experiences with banning antimicrobials used for growth promotion in food-producing animals suggest that, although the U.S. pork and poultry industries may experience minor economic impacts from similar bans (such as those proposed under PAMTA), management strategies may help overcome some of these costs in animal mortality and feed conversion. Further, the European experience shows that a ban can be successful from a public health perspective in reducing the percent of bacteria isolated from animals and foods that are resistant to antimicrobials.[322] Even bans as broad as those performed in Europe, however, may improve but will not fully eliminate the problem of antimicrobial resistance, particularly considering the global nature of antimicrobial use in multiple industries. The next Part will detail how regulatory and legislative bodies must consider that any use of antimicrobials can select for resistance and will provide recommendations on building a regulatory framework and supporting public health efforts to better address this international problem.

VI. SCIENTIFIC CRITIQUE OF EXISTING AND PROPOSED REGULATIONS

Because antimicrobial-resistant infections pose an urgent and global public health threat, the question that remains is not whether action should be taken on a regulatory front, but how best to accomplish the goal of restricting the spread and impact of antimicrobial resistance.

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318. Council Directive 2003/99, 2003 O.J. (L 325) 31 (EC).

319. Anno de Jong et al., *A Pan-European Survey of Antimicrobial Susceptibility Towards Human-Use Antimicrobial Drugs Among Zoonotic and Commensal Enteric Bacteria Isolated from Healthy Food-Producing Animals*, 63 J. ANTIMICROBIAL CHEMOTHERAPY 733, 734 (2009).

320. *Id.* at 742-43 (noting that few resistance patterns following the bans returned to zero, and also that some resistance patterns (e.g., to streptogramins and fluoroquinolones) remain higher than expected); *see infra* Part VI.B.

321. *See* P.M. Hawkey, *The Growing Burden of Antimicrobial Resistance*, 62 J. ANTIMICROBIAL CHEMOTHERAPY i1, i5 (Supp. 2008); Joseph F. John, Jr. & Neil O. Fishman, *Programmatic Role of the Infectious Diseases Physician in Controlling Antimicrobial Costs in the Hospital*, 24 CLINICAL INFECTIOUS DISEASES 471, 472 tbl.1 (1997).

322. U.S. GEN. ACCOUNTING OFFICE, *supra* note 29, at 19-20.

Addressing judicious use in human clinical settings is important, and furthering development of novel antimicrobial drugs and alternative therapies is critical.[323] In addition, as the case of virginiamycin demonstrated,[324] new antimicrobials intended for human clinical use should neither be first nor concurrently licensed for growth promotion uses. Further, given the economic disincentives for research and development on new antimicrobials, regulatory effort is needed urgently to protect the current arsenal of drugs.[325] Addressing use of antimicrobials in agriculture presents an opportunity for science-based intervention through regulation and policy.[326]

A. Critically Important Antimicrobials

Both European and proposed U.S. regulatory strategies to address antimicrobial resistance focus on "critically important antimicrobials," also known as "medically important antibiotics," or those antimicrobials used in human clinical settings to treat known pathogens.[327] Some have called this a "one bug, one drug" model.[328] However, this approach has several critical limitations.

First, antimicrobial resistance is not limited to pathogens, and resistance in commensal (nonpathogenic) bacteria can spread to pathogens in bacterial communities.[329] Because both pathogens and nonpathogens may acquire and exchange genes that confer resistance, surveillance systems like NARMS, limited to a few bacteria, primarily foodborne pathogens, may miss important pools of resistant commensal bacteria and nontested pathogens (e.g., *Staphylococcus aureus*).[330] A key recommendation of this Article is to expand surveillance systems to include both commensal and pathogenic bacteria, and to include nonfood

323. *See supra* Part II.B.

324. *See supra* Part V.B.

325. Boucher et al., *supra* note 167, at 1.

326. Aarestrup et al., *supra* note 92 (reviewing options for strategies to control antimicrobial resistance and their anticipated effectiveness from a scientific perspective).

327. *See generally* Collignon et al., *supra* note 307.

328. Silbergeld et al., *supra* note 10, at 156 (citing Anne O. Summers, *Genetic Linkage and Horizontal Gene Transfer, the Roots of the Antibiotic Multi-Resistance Problem*, 17 ANIMAL BIOTECHNOLOGY 125 (2006)).

329. Keyes et al., *supra* note 42, at 45-51; Skippington & Ragan, *supra* note 65, at 711-12.

330. In an October 12, 2010, letter to Representative Louise Slaughter, the FDA noted that NARMS personnel are exploring the possibility of adding *S. aureus* to the list of tested organisms. Letter from Jeanne Ireland, Assistant Comm'r for Legislation, FDA, to Representative Louise Slaughter, U.S. House of Representatives (Oct. 12, 2010), http://www.keepantibioticsworking.com/new/KAWfiles/64_2_107766.pdf.

pathways, such as occupational health monitoring[331] for potential transmission of resistant zoonoses to humans.[332] Occupational transmission of MRSA to veterinarians,[333] farmers,[334] and slaughter workers[335] has been demonstrated. A particular MRSA strain, ST398,[336] was found in food animals, especially pigs, and may be transmitted to humans.[337] This strain commonly carried a plasmid encoding for multiple resistance genes to different classes of antimicrobials, including tetracycline.[338]

In addition, as Dr. Nancy Halpern noted in her previous review, reservoirs for resistant bacteria may occur in many species.[339] This includes humans, food-producing animals, companion animals (e.g., dogs, cats, and horses), and occasionally exotic or wild animals.[340] Companion animals, to date, have not been part of routine monitoring programs for antimicrobial resistant bacteria,[341] despite research evidence that demonstrates trends of sometimes high rates of resistant bacteria in these populations.[342] Many human families consider companion animals as part of their households,[343] and antimicrobial-resistant infections may

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331. Ricardo Castillo et al., Antimicrobial-Resistant Bacteria: An Unrecognized Work-Related Risk in Food Animal Production 1 (2011) (unpublished manuscript) (on file with author).

332. *See* J. Scott Weese, *Prudent Use of Antimicrobials*, *in* ANTIMICROBIAL THERAPY IN VETERINARY MEDICINE, *supra* note 178, at 437, 445.

333. A. Loeffler et al., *Meticillin-Resistant* Staphylococcus Aureus *Carriage in UK Veterinary Staff and Owners of Infected Pets: New Risk Groups*, 74 J. HOSP. INFECTION 282, 283 (2010).

334. Tara C. Smith et al., *Methicillin-Resistant* Staphylococcus Aureus *(MRSA) Strain ST398 Is Present in Midwestern U.S. Swine and Swine Workers*, 4 PLOS ONE e4258 (2009).

335. *See* M.N. Mulders et al., *Prevalence of Livestock-Associated MRSA in Broiler Flocks and Risk Factors for Slaughterhouse Personnel in the Netherlands*, 138 EPIDEMIOLOGY & INFECTION 743 (2010); B.A.G.L. van Cleef et al., *High Prevalence of Nasal MRSA Carriage in Slaughterhouse Workers in Contact with Live Pigs in the Netherlands*, 138 EPIDEMIOLOGY & INFECTION 756 (2010).

336. This strain designation, known as ST398, was originally called NT-MRSA.

337. *See* Abby L. Harper et al., *An Overview of Livestock-Associated MRSA in Agriculture*, 15 J. AGROMEDICINE 101, 103 (2010).

338. Kristina Kadlec & Stefan Schwarz, *Novel ABC Transporter Gene,* vga*(C), Located on a Multiresistance Plasmid from a Porcine Methicillin-Resistant* Staphylococcus Aureus *ST398 Strain*, 53 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 3589, 3589 (2009).

339. *See* Halpern, *supra* note 33, at 8-24.

340. *See* Weese, *supra* note 332, at 437, 445.

341. *Id.*

342. *See* Bruno B. Chomel & Ben Sun, *Zoonoses in the Bedroom*, 17 EMERGING INFECTIOUS DISEASES 167, 170 (2011) (citing Farrin A. Manian, *Asymptomatic Nasal Carriage of Mupirocin-Resistant* Staphylococcus Aureus *(MRSA) in a Pet Dog Associated with MRSA Infection in Household Contacts*, 36 CLINICAL INFECTIOUS DISEASES e36 (2003)); A. Loeffler & D.H. Lloyd, *Companion Animals: A Reservoir for Methicillin-Resistant* Staphylococcus Aureus *in the Community?*, 138 EPIDEMIOLOGY & INFECTION 595 (2010); E. van Duijkeren et al., *Methicillin-Resistant* Staphylococcus Aureus *in Horses and Horse Personnel: An Investigation of Several Outbreaks*, 141 VETERINARY MICROBIOLOGY 96 (2010).

343. Chomel & Sun, *supra* note 342, at 167.

spread between humans and their animal companions.[344] National recommendations are warranted for harmonization between human medical and veterinary practice for community surveillance, treatment for antimicrobial-resistant infections within and among households, and judicious use of antimicrobial drugs.[345] At minimum, integrating healthcare surveillance networks, such as NHSN,[346] with other national databases like NARMS would allow better tracking of the movement of resistance determinants and resistant pathogens between the community and the hospital.[347] Ideally, establishment of a veterinary clinical surveillance system, integrated with human healthcare networks, would help quantify the role of companion animal antimicrobial therapies in selecting for household-level resistance. This information could guide recommendations for judicious use practices in both veterinary and human medicine. In addition, expansion of monitoring systems to include rural community hospitals, which typically do not participate in antimicrobial stewardship programs or surveillance networks,[348] would allow better tracking of potential community exposure to antibiotic pollution that may occur through environmental pathways in rural areas.

Finally, and most important, use of antimicrobials not considered "medically important" may co-select for bacteria resistant to drugs used in human clinical settings.[349] In other words, the use of one allowed antimicrobial in livestock may drive resistance to an antimicrobial restricted to human use.[350] This is a key limitation of the PAMTA approach, which focuses on "critical antimicrobial animal drugs."[351] Within the beta-lactam class of antimicrobials, PAMTA would restrict only penicillins, allowing use of cephalosporins known to select for beta-

344. Manuel Bramble et al., *Potential Role of Pet Animals in Household Transmission of Methicillin-Resistant* Staphylococcus Aureus*: A Narrative Review*, 11 VECTOR-BORNE & ZOONOTIC DISEASES 617, 617 (2011).

345. The agenda of the Antimicrobial Resistance Summit (2011) was integrating surveillance and regulation with infection prevention activities in multiple settings and with education and research efforts. Thomas Gottlieb & Graeme R. Nimmo, *Antibiotic Resistance Is an Emerging Threat to Public Health: An Urgent Call to Action at the Antimicrobial Resistance Summit 2011*, 194 MED. J. AUSTL. 281, 281 fig.1 (2011).

346. *See supra* Part III.B.

347. Silbergeld et al., *supra* note 68, at 1392-93.

348. Birgir Johannsson et al., *Improving Antimicrobial Stewardship: The Evolution of Programmatic Strategies and Barriers*, 32 INFECTION CONTROL & HOSP. EPIDEMIOLOGY 367, 372 (2011) (regarding the need to include small community hospitals in computerized networks and provide other incentives for participation in antimicrobial stewardship programs).

349. *See* Gottlieb & Nimmo, *supra* note 345, at 281.

350. This may occur because the genes for resistance may co-locate to the same mobile genetic element. *See* Silbergeld et al., *supra* note 68, at 1394-95.

351. *See* Preservation of Antibiotics for Medical Treatment Act of 2011, H.R. 965, 112th Cong. § 4 (2011).

lactam-resistant bacteria (e.g., the "superbug" MRSA).[352] Recent action by the FDA, however, limited certain extralabel uses of cephalosporins in food-producing animals.[353] For example, a banned extralabel agricultural use of cephalosporins noted by the FDA[354] to be of great concern is the routine injection into chicken eggs prior to hatch.[355] To be effective at limiting selective pressure for beta-lactam resistance, both penicillins and cephalosporins need to be restricted simultaneously.

All antimicrobials, including those approved before 2003,[356] and including those not considered critically important by the World Health Organization, should be evaluated for the potential to induce resistance to a broad spectrum of antimicrobial drugs in a range of bacteria. Some mechanisms of resistance may be broad.[357] Even more concerning, some metals (e.g., zinc),[358] and nonantimicrobial pharmaceuticals (e.g., aspirin, a salicylate),[359] also may play important roles in selecting for resistant organisms or promoting resistance mechanisms. While the extent of the ability of nonantimicrobials to select for antimicrobial-resistant bacteria is not yet well-characterized, improved reporting of all drugs (not just certain antimicrobial drugs) used in food-producing animals will allow better monitoring of this potential phenomenon.

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352. *See* Preservation of Antibiotics for Medical Treatment Act of 2011, S. 1211, 112th Cong. § 4 (2011).

353. Extralabel Drug Use in Animals, 21 C.F.R. § 530.1 (2011); *see supra* text accompanying note 95.

354. Jennifer L. Davis et al., *Update on Drugs Prohibited from Extralabel Use in Food Animals*, 235 J. AM. VETERINARY MED. ASS'N 528, 532-33 (2009) (concerning prohibited extralabel uses; others may be allowed).

355. J.L. McReynolds et al., *The Effect of In Ovo or Day-of-Hatch Subcutaneous Antibiotic Administration on Competitive Exclusion Culture (PREEMPT™) Establishment in Neonatal Chickens*, 79 POULTRY SCI. 1524, 1525 (2000).

356. *See supra* Part III.C.

357. Certain drug efflux pumps will provide resistance to multiple families of antibiotics. In addition, other characteristics, such as the thickness of a cell wall, may help exclude antibiotics from a bacterium, conferring partial resistance. The latter is one mechanism of action for partial vancomycin resistance in some MRSA isolates. Benjamin P. Howden et al., *Reduced Vancomycin Susceptibility in* Staphylococcus Aureus*, Including Vancomycin-Intermediate and Heterogeneous Vancomycin-Intermediate Strains: Resistance Mechanisms, Laboratory Detection, and Clinical Implications*, 23 CLINICAL MICROBIOLOGY REV. 99, 107-08, 109 tbl.3 (2010).

358. Lina M. Cavaco et al., *Zinc Resistance of* Staphylococcus Aureus *of Animal Origin Is Strongly Associated with Methicillin Resistance*, 150 VETERINARY MICROBIOLOGY 344, 344, 347 (2011).

359. *See* Zhangqi Shen et al., *Salicylate Functions as an Efflux Pump Inducer and Promotes the Emergence of Fluoroquinolone-Resistant* Campylobacter Jejuni *Mutants*, 77 APPLIED & ENVTL. MICROBIOLOGY 7128 (2011).

B. Anticipated Impact of Regulation on Resistance

Surveillance and regulation do not occur in a vacuum; the intent of these programs is to produce a beneficial effect for society. Understanding how changes in regulation of antibiotics will impact the epidemic of antimicrobial resistance requires a scientific understanding of the microbial ecology of resistance, as this Article has reviewed.[360] While the experience of regulatory authorities in Europe offers a model for a generally successful public health intervention, other antimicrobial restrictions, such as the fluoroquinolone ban in poultry in the United States, have achieved less success in the short term from a public health perspective.

Resistance to ciprofloxacin has persisted despite the ban on fluoroquinolones.[361] Data from the NARMS surveillance program demonstrated a lack of immediate improvement in ciprofloxacin resistance in chickens, chicken breasts, and human isolates of the important foodborne pathogen *Campylobacter jejuni*[362] following the 2005 ban on fluoroquinolone use.[363] A simple analysis of these data reveals a 3% increase, on average, of ciprofloxacin resistance in *C. jejuni* isolates from these sources after the ban (2006-2009) compared to before the ban (2002-2005).[364] U.S. researchers also have noted the lack of

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360. *See supra* Part II.

361. Ramakrishna Nannapaneni et al., *Ciprofloxacin-Resistant* Campylobacter *Persists in Raw Retail Chicken After the Fluoroquinolone Ban*, 26 FOOD ADDITIVES & CONTAMINANTS 1348, 1348, 1352 (2009); *see supra* Part III.F.

362. *Campylobacter jejuni* may colonize chickens at high rates without causing disease, making contamination of food products more likely. *See generally* B.A. McCrea et al., *Prevalence of* Campylobacter *and* Salmonella *Species on Farm, After Transport, and at Processing in Specialty Market Poultry*, 85 POULTRY SCI. 136 (2006). *Campylobacter* is a leading cause of foodborne illness in the United States, responsible for an estimated two million human infections annually. Michael C. Samuel et al., *Epidemiology of Sporadic* Campylobacter *Infection in the United States and Declining Trend in Incidence, FoodNet 1996-1999*, 38 CLINICAL INFECTIOUS DISEASES S165 (Supp. 2004).

363. FDA, NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM: 2009 EXECUTIVE REPORT 82 tbl.50b (2011), http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM268954.pdf; Zhao et al., *supra* note 188, at 7951 & fig.1 (noting a trend in ciprofloxacin resistance).

364. This simple analysis was performed by the author (MFD). Methods: Briefly, data on the proportion of resistant isolates, by type and year, were adapted from the NARMS 2009 (FDA, *supra* note 363) report to Stata 11 (College Station, TX). A linear regression model was run on the proportion of ciprofloxacin resistance compared to a dichotomous variable (after vs. before the ban) for time trend, and clustering within type of isolate (human, chicken breast, and chickens). Results: After the ban, on average, the proportion of ciprofloxacin resistance increased 0.029 (~3%), and this estimate was statistically significant (p=0.008). No statistical differences were seen by type of isolate, controlling for year (p=0.36). Overall averages for percentage of ciprofloxacin resistance found since the ban (for humans, chicken breasts, and

reduction in fluoroquinolone resistance in poultry isolates following the ban.[365] NARMS retail data from 2009 support a statistically significant 5.9% increase in fluoroquinolone resistant *C. jejuni* from retail meats between 2002 and 2009.[366] In Europe, even after the bans on growth promoters, high rates of fluoroquinolone resistance were found in *Campylobacter* and other bacterial species in both humans and poultry, but in Australia, where fluoroquinolones never were approved for food-producing animal use, cases of domestically acquired human ciprofloxacin-resistant *Campylobacter* have been rare.[367]

Multiple potential mechanisms may explain this persistence. First, in the United States, fluoroquinolones were restricted only in poultry, and use was allowed to continue in other species, such as cattle.[368] Second, international shipment of food products and global human travel may spread resistant strains and resistance determinants beyond the boundaries of regulation. A pandemic ciprofloxacin-resistant clone of *Salmonella enterica* Serotype Kentucky was found in both humans and chickens, and use of fluoroquinolones in poultry production in Nigeria and Morocco was implicated in the rapid international spread of the pathogen.[369] Third, contrary to historical scientific belief that resistance genes are burdensome to bacteria,[370] certain genes may not be jettisoned quickly once selective pressure is reduced.[371] Finally, as noted above, cross-resistance within bacteria to multiple drugs may allow nontarget antimicrobials to provide selective pressure.[372] Of note, tetracycline drugs,

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chickens combined) were: 21.3% (2009), 23.0% (2008), 21.5% (2007), and 14.9% (2006). *See* FDA, *supra* note 363, at 82 tbl.50b.

365. Lance B. Price et al., *The Persistence of Fluoroquinolone-Resistant* Campylobacter *in Poultry Production*, 115 ENVTL. HEALTH PERSP. 1035, 1037 (2007); Nannapaneni et al., *supra* note 361.

366. FDA, NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM: 2009 RETAIL MEAT REPORT 9 (2009), http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM257587.pdf.

367. Ulrich Löhren et al., *Guidelines for Antimicrobial Use in Poultry*, *in* GUIDE TO ANTIMICROBIAL USE IN ANIMALS 126, 132-33 (Luca Guardabassi et al. eds., 2008) (citing Leanne Unicomb et al., *Fluoroquinolone Resistance in Campylobacter Absent from Isolates, Australia*, 9 EMERGING INFECTIOUS DISEASES 1482 (2003)).

368. *See Animal & Veterinary: CVM Approves Fluoroquinolone Product for Use in Cattle*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm089486.htm (last updated Oct. 28, 2009).

369. Simon Le Hello et al., *International Spread of an Epidemic Population of* Salmonella Enterica *Serotype Kentucky ST198 Resistant to Ciprofloxacin*, 204 J. INFECTIOUS DISEASES 675, 681 (2011).

370. *See* LAXMINARAYAN ET AL., *supra* note 68, at 50.

371. Silbergeld et al., *supra* note 10, at 156-57 (citing Qijing Zhang, *Fitness of Antimicrobial-Resistant* Campylobacter *and* Salmonella, 8 MICROBES & INFECTION 1972 (2006)).

372. *See supra* Part VI.A.

used widely in food animal production, are known to select for fluoroquinolone resistance.[373] Data from NARMS in 2009 show 50% tetracycline resistance in chicken isolates of *Campylobacter*, 46% resistance in chicken product isolates, and 43% resistance in human isolates.[374] The degree to which other pharmaceutical products, such as aspirin, promote fluoroquinolone resistance is unknown.[375] Whether resistance (e.g., to fluoroquinolones) that is easy to induce is more likely to persist also is unknown.

An additional concern with the fluoroquinolone ban was, paradoxically, the strength of the scientific evidence used for its support. The risk assessment conducted by the FDA demonstrated a strong connection between use of a particular antimicrobial in poultry and emergence of resistance patterns in the same family of antimicrobial in humans.[376] Industry[377] and members of Congress[378] have suggested that, for regulation to occur, regulatory authorities must prove that use of antimicrobials at nontherapeutic levels caused resistance in a particular bacterium, and that this specific bacterium was transmitted to humans.

Causation is difficult to prove in science, particularly in as dynamic a setting as antimicrobial resistance. Multiple sources can contribute to the problem, but proof that any one pathway was the cause for a particular case of disease in a particular individual is challenging.[379] Any and all uses of antimicrobials may contribute to selective pressure,

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373. *See, e.g.*, Seth P. Cohen et al., *Cross-Resistance to Fluoroquinolones in Multiple-Antibiotic-Resistant (Mar)* Escherichia Coli *Selected by Tetracycline or Chloramphenicol: Decreased Drug Accumulation Associated with Membrane Changes in Addition to OmpF Reduction*, 33 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1318, 1320 (1989).

374. FDA, *supra* note 363, at 82 tbl.50b. Data on cross-resistance, however, is not available in published reports, which provide only prevalences of resistance in particular pathogens by source, i.e., food animals, retail meat, or humans.

375. *See* Shen et al., *supra* note 359, at 7129, 7131.

376. CTR. FOR VETERINARY MED., *supra* note 203, at I-1 to -3.

377. *See* Kiser, *supra* note 107, at 1062.

378. Letter from Representative Tom Latham, U.S. House of Representatives, to Lester M. Crawford, Acting Comm'r, FDA (Sept. 1, 2004), http://www.fda.gov/ohrms/dockets/dockets/00n1571/00n-1571-m000006-vol403.pdf (suggesting that the FDA should have "scientific certainty" to ban fluoroquinolone use).

379. This is similar to the burden of ascribing a "cause" for cancer in a particular individual suffering from its effects, particularly when the cancer is potentially linked to many sources (e.g., diet, smoking habits, chemical exposures, and genetics). However, chemicals and commercial products (e.g., cigarettes) have been regulated despite this difficulty. Further, for chemicals, in vitro (cell culture) and in vivo (laboratory animal) assays demonstrating carcinogenicity in the laboratory prove sufficient for risk assessment purposes. On the contrary, similar laboratory and field assays demonstrating the ability of antibiotics to select for resistance and promote transfers of genetic material in bacteria conferring resistance are attacked by opponents of regulation as insufficient evidence of harm. *See* Cummings, *supra* note 150, at 209-10.

including therapeutic uses in both human and veterinary hospital environments.[380] In addition, soil organisms and other microbes may produce antibiotics at very low concentrations,[381] although public health impacts from these natural sources may be limited. Both humans and animals may carry bacteria, including zoonotic pathogens, that harbor genes for antimicrobial resistance.[382] Isolating agriculture as the specific cause of any given human case of MRSA or *Salmonella* requires expensive molecular testing at all stages of transmission, which typically is not performed in either surveillance or clinical settings.[383] For the fluoroquinolone ban, molecular evidence was provided that linked strains of fluoroquinolone-resistant bacteria in food products to the same strains in human cases of disease.[384] This "high bar" set by the fluoroquinolone ban offers a barrier to regulation of antimicrobials whose effects are harder to demonstrate. In its recent order of prohibition for certain extralabel uses of cephalosporins, the FDA addressed this perception of a need to conduct a risk assessment and prove that an adverse event has occurred in humans in order to take regulatory action, noting instead that "it is not limited to making risk determinations based solely on documented scientific information, but may use other suitable information as appropriate."[385]

The complex ecology of bacterial resistance also impacts interpretation of the public health success or failure of regulation. In some cases, broad use of an antimicrobial, such as in medicated animal

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380. *See* Carlene A. Muto et al., *SHEA Guideline for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of* Staphylococcus Aureus *and* Enterococcus, 24 INFECTION CONTROL & HOSP. EPIDEMIOLOGY 362, 362-63 (2003).

381. Wright, *supra* note 49, at 184. After all, Fleming discovered penicillin by isolating it from the mold *Penicillium*.

382. *See* David H. Lloyd, *Reservoirs of Antimicrobial Resistance in Pet Animals*, 45 CLINICAL INFECTIOUS DISEASES S148, S151 (Supp. 2007); Christiane Cuny et al., *Emergence of Methicillin-Resistant* Staphylococcus Aureus *(MRSA) in Different Animal Species*, 300 INT'L J. MED. MICROBIOLOGY 109, 109 (2010).

383. *See* Petra Mullner et al., *Assigning the Source of Human Campylobacteriosis in New Zealand: A Comparative Genetic and Epidemiological Approach*, 9 INFECTION GENETICS & EVOLUTION 1311 (2009). In this study, surveillance and laboratory data were combined, and isolates tested using molecular techniques, to determine that most cases of human campylobacteriosis were attributable to poultry. Government intervention in poultry production practices led to a decline in human cases. New Zealand's relative isolation—as an island country—likely enhanced the determination of cause. *See id.*

384. Smith et al., *supra* note 194, at 1526-31.

385. New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition, 77 Fed. Reg. 735, 743 (Jan. 6, 2012) (to be codified at 21 C.F.R. pt. 530) (quoting Extralabel Drug Use in Animals, 61 Fed. Reg. 57,732, 57,738 (Nov. 7, 1996)). At the time of writing, this order of prohibition was still in public comment and was scheduled to take effect in April, 2012. *Id.* at 735.

feed or water, may open a veritable "Pandora's box" of resistance.[386] Subsequent attempts to reduce usage, particularly when the reduction in use is limited to one or several countries, or limited only in a single species of food-producing animal, may be less successful than anticipated. In these cases, broader restrictions may be needed, and restrictions on multiple drugs, not just the target antimicrobial, should be explored. In the case of fluoroquinolones, some evidence links tetracycline to selection for fluoroquinolone resistance,[387] suggesting the potential need to restrict more than one class of antimicrobial to achieve the public health target effect.

C. Environmental Pollution

Many bacteria and their genes for resistance can survive in the environment.[388] Industries involved in antimicrobial manufacture, trade, and usage—from pharmaceutical companies to agribusiness to medical enterprises—are connected through environmental pathways. Effluent into surface waters from an antimicrobial manufacturing plant was found to drive selection for antimicrobial resistance in bacteria found downstream.[389] Use of antimicrobials in food-producing animals on farms has been tied to contamination of local and regional soils and waters.[390] Human and animal use may result in discharge of drugs into sewage,[391] leading to contamination of surface water.[392] Manures and animal by-products that contain antimicrobial residues may enter other industries through sale or trade.[393] As a result, both animals and humans may unintentionally consume antimicrobials through drinking water or other sources as a result of contamination of those sources.[394] This evidence makes antimicrobial pollution in the environment important to consider as a future regulatory target.

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386. Goforth & Goforth, *supra* note 33, at 68-70.

387. Cohen et al., *supra* note 373, at 1320.

388. Davis et al., *supra* note 56, at 247-48.

389. Dong Li et al., *Antibiotic Resistance Characteristics of Environmental Bacteria from an Oxytetracycline Production Wastewater Treatment Plant and the Receiving River*, 76 APPLIED & ENVTL. MICROBIOLOGY 3444, 3444-45 (2010).

390. Love et al., *supra* note 78, at 279 (citing Jay P. Graham et al., *Fate of Antimicrobial-Resistant Enterococci and Staphylococci and Resistance Determinants in Stored Poultry Litter*, 109 ENVTL. RES. 682 (2009)); Davis et al., *supra* note 56, at 246-48.

391. *See* David W. Graham et al., *Antibiotic Resistance Gene Abundances Associated with Waste Discharges to the Almendares River near Havana, Cuba*, 45 ENVTL. SCI. & TECH. 418 (2011).

392. *See* Kyunghee Ji et al., *Influence of Water and Food Consumption on Inadvertent Antibiotics Intake Among General Population*, 110 ENVTL. RES. 641, 646 (2010).

393. Graham & Nachman, *supra* note 88, at 653-54; Love et al., *supra* note 91.

394. Ji et al., *supra* note 392, at 646.

The Task Force has been a multiagency effort, and has included participation by the EPA, the agency most likely to spearhead future regulation of antimicrobials in the environment. Indeed, recommendations in the *Action Plan* included plans to consider environmental impacts.[395] Strategies to address antimicrobial chemical pollution discharged into the environment, however, need to account for the diverse reservoir of resistance genes found in native soil microorganisms.[396] Because genes for resistance can be found broadly in the environment, attempts to reduce environmental antimicrobial pollution may need to be equally broad, targeting both point and nonpoint sources of antimicrobial discharge simultaneously. Consideration of antimicrobial pollution may require novel risk assessment techniques. In contrast to most regulated chemicals, which do not multiply in the environment, even low concentrations of antimicrobials may drive selective pressure for antimicrobial resistance, expanding the local reservoir of resistance genes.[397] This is in contrast to a traditional EPA assessment, which often assumes a threshold below which adverse effects are assumed to be negligible.[398]

Current scientific evidence is insufficient to quantify the role of environmental antimicrobial pollution in driving the epidemic of antimicrobial resistance, and it is equally insufficient to allow accurate prediction of the scope of regulation that might be needed to achieve a public health benefit. As a result, a first step toward consideration of how this reservoir might be regulated should involve expansion of surveillance programs and research funding, followed by testing potential regulatory efforts in carefully chosen ecosystems through pilot intervention programs at the local or state level. In the meantime, educational efforts could target reduction of antimicrobial contamination that occurs at known sources, such as on CAFOs. For example, researchers recently have shown that poultry farms that transitioned from conventional to organic (no antimicrobial use) practices had significantly lower prevalence of resistance in *Enterococci* bacteria found in litter, feed, and water compared to conventional farms that used

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395. Interagency Task Force on Antimicrobial Resistance, *supra* note 130, at 30 (discussing the role of the EPA in antibiotic and antibiotic pesticide registrations).

396. *See* Wright, *supra* note 49.

397. Love et al., *supra* note 78, at 280 & fig.1.

398. *See* NAT'L RESEARCH COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT 127-28 (2009).

antimicrobials.[399] Strategies could include incentives to support organic practices and regulatory support of improved veterinary oversight of antimicrobial use in food-producing animals, particularly use in medicated feed and water.

D. Veterinary Oversight

Currently, veterinary involvement in antimicrobial use on the farm is low, and this lack of oversight may lead to inappropriate use of antimicrobials by producers.[400] Research through the National Animal Health Monitoring System (NAHMS) for dairy operations showed that producers consulted a veterinarian only 46% of the time before choosing an antimicrobial, and they based their antimicrobial choice on culture and sensitivity results only 20% of the time.[401] In 2001, the *Action Plan* made the following two recommendations, to be implemented through the coordination of the FDA and USDA:

> (59) Strongly encourage involvement of veterinarians in decisions regarding the use of systemic antimicrobial drugs in animals, regardless of the distribution system through which the drug is obtained (e.g., regardless of whether a prescription is required to obtain the drug). . . .
> (60) Evaluate the potential impact of making all systemic veterinary antimicrobial drugs available by prescription only.[402]

As previously noted,[403] the AVMA has voiced concerns with the burden such oversight would place on the inadequate food-producing animal veterinary workforce.[404] This demonstrates the need to harmonize regulations and legislation addressing antimicrobial usage with support for the scientific expertise and occupational resources needed to accomplish the goals of any federal directive.[405] Veterinary training

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399. Amy R. Sapkota et al., *Lower Prevalence of Antibiotic-Resistant Enterococci on U.S. Conventional Poultry Farms that Transitioned to Organic Practices*, 119 ENVTL. HEALTH PERSP. 1622, 1622 (2011).

400. *See* Goforth & Goforth, *supra* note 33 (discussing veterinarians' current role and suggesting changes).

401. USDA, DAIRY 2007—PART III: REFERENCE OF DAIRY CATTLE HEALTH AND MANAGEMENT PRACTICES IN THE UNITED STATES, 2007, at 141 (Sept. 2008), http://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy07/Dairy07_dr_PartIII_rev.pdf.

402. Interagency Task Force on Antimicrobial Resistance, *supra* note 130, at 30.

403. *See supra* Part III.D.

404. *See* Letter from W. Ron DeHaven to FDA, *supra* note 168.

405. At the time of writing, only one specific federal incentive existed to support entry of veterinarians into food animal practice, public practice, and research. The Veterinary Medicine Loan Repayment Act (VMLRP) is a small program to help provide partial repayment of educational loans, but only in specific, designated shortage areas that require nomination by state health officials. *See Animal Health: The Veterinary Medicine Loan Repayment Program*

systems, such as the National Veterinary Accreditation Program (NVAP) through USDA,[406] could be one venue through which national recommendations are harmonized. In return, food animal veterinarians could serve as consultants to large producers (CAFOs) to assist with programs to reduce antimicrobial usage and also to help these producers accurately report such usage to state and federal authorities.

E. Surveillance for Antimicrobial Usage

Improving transparency of antimicrobial usage, particularly in the livestock and pharmaceutical industries, is critical for future regulatory and surveillance efforts. Although the FDA recently published the inaugural summaries of antimicrobial distribution for use in food-producing animals,[407] data that are collected by the FDA on specific indications for usage (i.e., disease conditions by species), species, or month of distribution are not in the public report.[408] Public provision of these data would harmonize reporting with that of NARMS, which is reported by species and month. Data on actual usage (i.e., amount consumed by species versus amount distributed to all food-producing animals) and geographic location of antimicrobial distribution (e.g., at the farm, zip code, county, or state level) are not collected, but could enhance surveillance efforts.[409] Even poultry industry veterinarians acknowledge the limitations this lack of data imposes on clinical, research, surveillance, and policy efforts.[410] Further, although USDA provides some public information on farm locations and farming practices in the United States,[411] its database is incomplete. This lack of information hinders regulatory, research, and surveillance efforts by

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(VMLRP), NAT'L INST. FOOD & AGRIC., U.S. DEP'T AGRIC., http://www.csrees.usda.gov/nea/animals/in_focus/an_health_if_vmlrp.html (last updated Jan. 19, 2012). The average veterinary student loan burden is $130,000, and the average starting salary is $65,000 and may be lower in rural areas. R. Scott Nolen, *Student Loan Subsidy's End Raises Concerns*, AM. VETERINARY MED. ASS'N (Sept. 15, 2011), http://www.avma.org/onlnews/javma/sep11/110915u.asp.

406. *See Animal Health: National Veterinary Accreditation Program (NVAP)*, ANIMAL & PLANT HEALTH INSPECTION SERV., U.S. DEP'T AGRIC., http://www.aphis.usda.gov/animal_health/vet_accreditation/ (last modified Mar. 5, 2012).

407. *See* CTR. FOR VETERINARY MED., *supra* note 18, at iv tbl.1.

408. *See id.* at 3 (providing specifications for reporting under the Animal Drug User Fee Act Amendments of 2008).

409. Meghan Davis, *More Data, Better Data: How FDA Could Improve the Animal Drug User Fee Act*, CENTER FOR A LIVABLE FUTURE BLOG (Nov. 15, 2011), http://www.livablefutureblog.com/2011/11/adufa-more-data-better-data (providing details of comments by the author (MFD) given during a public meeting at the FDA in Rockville, Maryland, on Nov. 7, 2011, regarding reauthorization of the ADUFA).

410. Cummings, *supra* note 150.

411. *See* USDA, *supra* note 11.

limiting the evidence base for public health conclusions. Open access to information could be used, not just as evidence to support antimicrobial restriction, but also as evidence to support a decision not to restrict certain individual antimicrobials or drug classes. European surveillance systems may offer models for expansion of data reporting in the United States.[412] Whether or not the FDA and other federal regulatory bodies have the political mandate, research capacity, and resources to expand surveillance, collect critical data, and implement new regulations is another consideration,[413] but one beyond the scope of this Article.

VII. CONCLUSION

In 2011, the World Health Organization dedicated its World Health Day to the global issue of antimicrobial resistance. Perhaps serendipitously, 2011 also marked World Veterinary Year.[414] Veterinarians are at the forefront of current regulatory efforts to address the problem of antimicrobial resistance—on both the side of the agencies attempting to promulgate regulations (the FDA's CVM) and also on the side of agribusiness (AVMA and others) attempting to limit regulatory restrictions on the use of antimicrobials in food-producing animals. Both sides call for a science-based approach to regulation.[415]

Understanding the science, specifically the ecology of antimicrobial resistance, underscores the need to better regulate nontherapeutic use of antimicrobials in food-producing animals.[416] Because movement of resistance genes can occur across national boundaries,[417] international strategies, and perhaps global regulatory authorities, are needed to address the emergence and transmission of antimicrobial resistance.[418] Within the United States, integration and harmonization of federal agency efforts, expansion of regulation of nontherapeutic antimicrobial

412. *See supra* Part V.C.

413. *See* Erik Stokstad, *Food Safety Law Will Likely Strain FDA Science*, 331 SCI. 270 (2011).

414. WORLD VETERINARY YEAR, www.vet2011.org (last visited Mar. 23, 2012).

415. *See generally* CTR. FOR VETERINARY MED., *supra* note 37 (discussing various scientific approaches); Letter from W. Ron DeHaven to FDA, *supra* note 168.

416. Possible exceptions could include antibiotics that have been tested for resistance and cross-resistance by multiple, independent researchers and proven not to be a threat to public health.

417. *See* Thomas F. O'Brien, *The Global Epidemic Nature of Antimicrobial Resistance and the Need To Monitor and Manage It Locally*, 24 CLINICAL INFECTIOUS DISEASES S2, S7 (Supp. 1997).

418. A key conclusion of the Australian Society for Infectious Diseases/Australian Society for Antimicrobials' Antimicrobial Resistance Summit (Feb. 7-8, 2011) was the need for "[a] national interdisciplinary body . . . to manage the looming antimicrobial resistance crisis." *See* Gottlieb & Nimmo, *supra* note 345, at 281.

use in food-producing animals, increased funding for research and surveillance of antimicrobial resistance, and mandates for public reporting of information critical to these programs will further domestic efforts to combat antimicrobial resistance. Failure of the current system to address growth promotion and similar nontherapeutic uses of antimicrobials in agriculture undermines federal efforts to control antimicrobial resistant infections in people, leading to a high economic cost and human burden of disease.[419] Although FDA currently has authority to regulate antimicrobial use in food animals, proposed legislation and existing regulatory efforts only partially address these public health concerns.[420]

Existing EU regulations and surveillance programs offer possible options for U.S. efforts to limit the nontherapeutic use of antimicrobials in livestock. Ultimately, efforts that consider the global ecosystem of resistance, including pathogenic and nonpathogenic bacteria and gene transfer among populations of bacteria, are critical to U.S. and global strategies to curb the rise of antimicrobial resistance.[421] On November 3, 2009, the White House released a joint US-EU declaration, which called for

> a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us.[422]

Bacteria do not respect national boundaries.[423] Scientific evidence should inform both the national regulatory strategies and the domestic and international surveillance systems that are important, not just to monitor the problem, but also to evaluate the impacts of regulation. The regulatory process itself should be guided by evidence of success, but such evidence should not be required *a priori* for new regulatory effort,

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419. *See* Coast & Smith, *supra* note 7, at 242.

420. *See* CTR. FOR VETERINARY MED., *supra* note 30; CTR. FOR VETERINARY MED., *supra* note 37; Preservation of Antibiotics for Medical Treatment Act of 2011, H.R. 965, 112th Cong. (2011); Preservation of Antibiotics for Medical Treatment Act of 2011, S. 1211, 112th Cong. (2011).

421. *See* Wright, *supra* note 49.

422. Press Release, Office of the Press Sec'y, The White House, U.S.-EU Joint Declaration and Annexes (Nov. 3, 2009), http://www.whitehouse.gov/the-press-office/us-eu-joint-declaration-and-annexes.

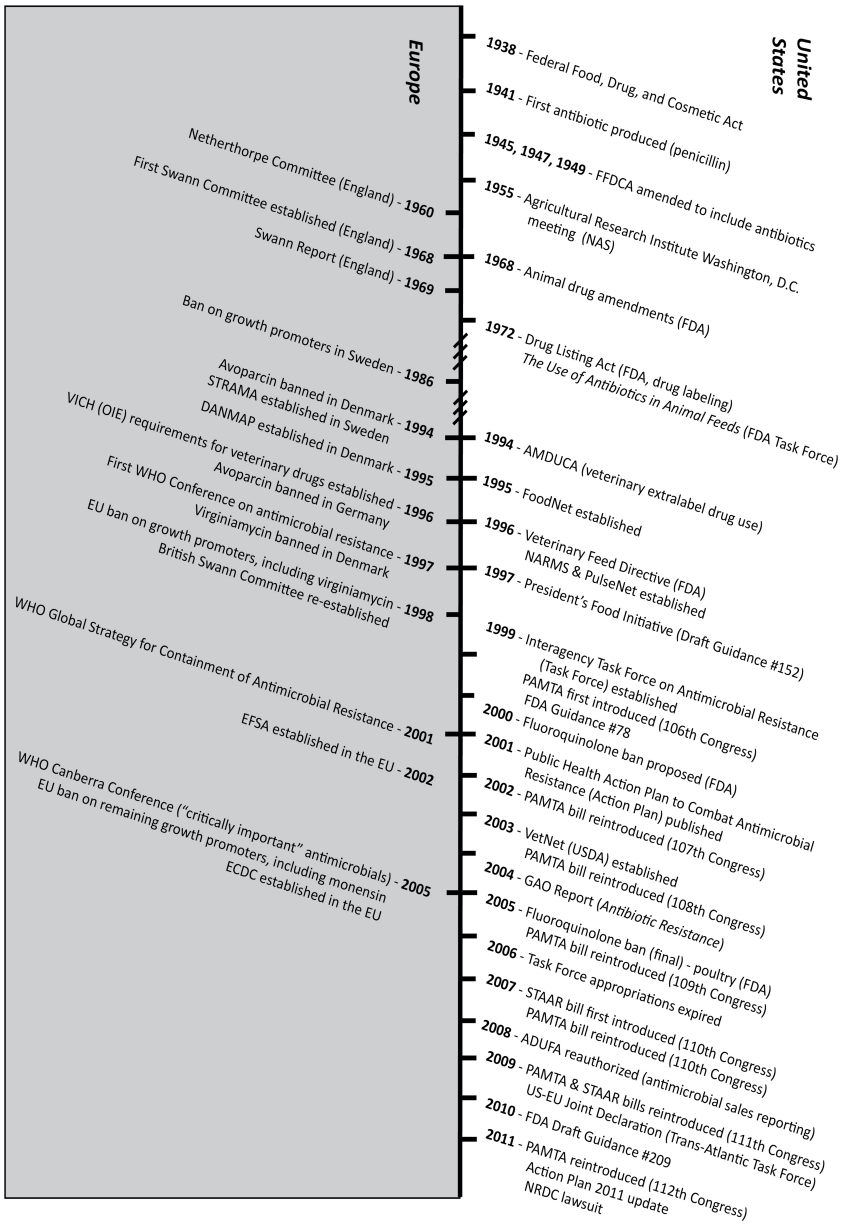
423. Stefan Monecke et al., *A Field Guide to Pandemic, Epidemic and Sporadic Clones of Methicillin-Resistant* Staphylococcus Aureus, 6 PLOS ONE e17936, at 2 (2011) (demonstrating international movement of clones of MRSA).

nor should incremental regulations be delayed.[424] Instead, policy-makers should focus on crafting regulation based on scientific evidence and providing for mechanisms of iterative evaluation of the public health impact of regulation.

We must intervene. The human, societal, and economic costs of drug-resistant infections are high. Given the complexity of the issue, a single regulation—a single target—is unlikely to be broadly successful. Imposing restrictions on use of antimicrobials in food-producing animals for growth promotion is one of many targets, and one that is scientifically easier to justify than it is politically feasible. This Article has demonstrated not just why, but how regulation can be informed by the current science. Long-term efforts grounded in scientific evidence are needed to harmonize use and restriction of use of antimicrobials internationally, and across multiple industries, particularly food animal production.

424. Incremental regulations should not be held to the same standards of evaluation as more comprehensive, multiagency regulatory efforts because partial or limited restrictions may be equally limited in their ability to achieve the desired public health effect.

APPENDIX I: REGULATORY TIMELINE



APPENDIX II: CRITICALLY IMPORTANT ANTIBIOTICS

Table of Selected Antibiotics by Class According to Human and Veterinary Use[425]

Antimicrobial Class	WHO Classification[426]	Human Antimicrobials		Veterinary Antimicrobials	
		Drug Example(s)	Use	Drug Example(s)	Use
Beta-Lactams					
*Penicillins***	Highly Important	Amoxicillin Cloxacillin	Tx	Amoxicillin Cloxacillin	Tx (FA, C) P (FA, C) GPA (FA)
Cephalosporins	Critically Important (3rd & 4th generation)	Ceftriaxone	Tx	Ceftiofur	Tx (FA, C) P (FA, C)
	Highly Important (1st & 2nd generation)	Cefazolin (Ancef) Cephalexin (Keflex)	Tx	Cephalexin	Tx (FA, C)
Glycopeptides	Critically Important	Vancomycin	Tx	Avoparcin§∅	GPA (FA)
Fluoroquinolones	Critically Important	Ciprofloxacin	Tx P (anthrax)	Enrofloxacin	Tx (FA, C) Extralabel FA use restricted
*Streptogramins***	Critically Important	Synercid (quinupristin-dalfopristin)	Tx	Virginiamycin∅	P (FA) GPA (FA)
Oxazolidinones	Critically Important	Linezolid	Tx	Linezolid	C use limited
*Tetracyclines***	Critically Important	Oxytetracycline Doxycycline	Tx	Oxytetracycline Chlortetracycline	Tx (FA, C) P (FA, C) GPA (FA)
*Macrolides***	Critically Important	Azithromycin Erythromycin Tylosin	Tx	Erythromycin Tylosin	Tx (FA, C) P (FA) GPA (FA)
*Sulfonamides***	Highly Important	Trimethoprim-sulfamethoxazole	Tx	Trimethoprim-sulfamethoxazole	Tx (FA, C) P (C)
*Lincosamides***	Important	Clindamycin Lincomycin	Tx	Clindamycin Lincomycin	Tx (FA, C) P (FA) GPA (FA)
*Aminoglycosides***	Critically Important	Amikacin Gentamicin	Tx	Amikacin Gentamicin	Tx (C) P (FA)

425. Table adapted from Collignon et al., *supra* note 307, at 139-40 tbl.4; Guardabassi & Courvalin, *supra* note 2, at 6-7 tbl.2; Angelo A. Valois et al., *Geographic Differences in Market Availability, Regulation and Use of Veterinary Antimicrobial Products*, *in* GUIDE TO ANTIMICROBIAL USE IN ANIMALS, *supra* note 367, at 59, 70-71 tbl.5.5.

426. FOOD & AGRIC. ORG. ET AL., JOINT FAO/WHO/OIE EXPERT MEETING ON CRITICALLY IMPORTANT ANTIMICROBIALS: REPORT OF THE FAO/WHO/OIE EXPERT MEETING 6 tbl.1 (2008), http://www.who.int/foodborne_disease/resources/Report_CIA_Meeting.pdf.

Antimicrobial Class	WHO Classification[426]	Human Antimicrobials		Veterinary Antimicrobials	
		Drug Example(s)	Use	Drug Example(s)	Use
		Kanamycin		Streptomycin Apramycin	GPA (FA)
Phenicols	N/A	Chloramphenicol	Limited uses (toxicity)	Florfenicol Chloramphenicol ✗	Tx (FA, C) P (FA) GPA (FA)

Table Legend

** PAMTA "medically important antibiotic"
§ Not typically used in the United States
∅ Banned in EU
✗ Banned in United States (and EU) for use in food-producing animals (never approved due to human health hazard)

Use Codes:
- Tx therapeutic uses
- P prophylaxis (treat individuals known or believed to be exposed to an infectious agent, or to prevent emergence of infection in food-producing animals, e.g., dairy cow treatment to prevent mastitis)
- GPA growth promotion

Species Codes:
- FA livestock (food-producing animals)
- C companion animals (dogs, cats, horses, etc.)