

RESISTING ANTIBIOTIC RESISTANCE: LEGAL STRATEGIES TO MAINTAIN MAN'S DOMINION OVER MICROBES

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I. INTRODUCTION

The discovery of practical and effective antibiotics in the mid 1940's led many to believe that infectious diseases were no longer a threat to human life.¹ Instead, the very use of these treatments has enhanced the biological phenomenon of antibiotic resistance and given rise to diseases that humans can no longer cure with antibiotics.² These diseases are called "superbugs," and they represent perhaps the greatest threat to global public health in the twenty-first century.³

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¹ See Ross Upshur, *Ethics and Infectious Diseases*, 86 BULL. WORLD HEALTH ORG. 654, 654 (2008) available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649475/> ("In an oft-quoted statement, the Surgeon General of the United States of America, William Stewart, said in 1967: 'The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States.'"); see also William M. Sage & David A. Hyman, *Combating Antimicrobial Resistance: Regulatory Strategies and Institutional Capacity*, 84 TUL. L. REV. 781, 784 (2010).

² See Jon Clardy et al., *The Natural History of Antibiotics*, 19 CURRENT BIOLOGY R437 (2009) ("Today, the evolution of antibiotic resistance by important human pathogens has rendered these original antibiotics and most of their successors largely ineffective..."); see also Richard D. Smith & Joanna Coast, *Resisting Resistance: Thinking Strategically About Antimicrobial Resistance*, 4 GEO. J. INT'L AFF. 135, 135 (2003).

³ Smith, *supra* note 2, at 135; see also Centers for Disease Control and Prevention, *Get Smart: Fast Facts About Antibiotic Resistance*, January 16, 2011, available at <http://www.cdc.gov/getsmart/antibiotic-use/fast-facts.html> ("Antibiotic resistance has been called one of the world's most pressing public health problems.").

While superbugs are a frightening reminder of the adaptability and ingenuity of microorganisms, they are also the direct result of mankind's chronic misuse and persistent overuse of antibiotics.⁴ Large public health organizations, such as the World Health Organization, have identified the persistent overuse of sub-optimal doses of antibiotics in animals as a primary source of antibiotic resistance.⁵ Improper use of antibiotics by medical professionals and patients also has a substantial impact on antibiotic resistance.⁶ These behaviors can be influenced by the legal system, and through the use of regulation, legislation, and punishment, the human impact on antibiotic resistance can be limited. This comment will discuss the potential legal solutions to the problem of antibiotic resistance. Specifically, this comment discusses potential modifications to intellectual property law, legislative initiatives, the use of tort damages to deter improper antibiotic use, and FDA regulation of antibiotics in animals and humans. The first section will discuss the biological and social foundations of antibiotic resistance. The second section will discuss the potential legal solutions to these problems.

⁴ See STUART B. LEVY, *THE ANTIBIOTIC PARADOX: HOW THE MISUSE OF ANTIBIOTICS DESTROYS THEIR CURATIVE POWERS* (2d ed. 2002) (arguing the persistent inappropriate use of antibiotics has threatened our ability to treat infectious diseases); see also Vanessa K. S. Briceno, *Superbug Me: The FDA's Role in the Fight Against Antibiotic Resistance*, 9 N.Y.U.J. INT'L L. & POL. 521, 523 (2005) (recognizing agricultural use of antibiotics as a significant contributor to antibiotic resistance).

⁵ See World Health Org., *Overcoming Antimicrobial Resistance: World Health Report on Infectious Diseases* 2000, http://www.who.int/infectious-disease-report/2000/other_versions/index_rpt2000_text.html (last visited Sep. 26, 2011) (observing that 50% of all antibiotics used in North America and Europe are used in feed for food-producing animals or poultry).

⁶ See *id.*; see also World Health Org., *Antimicrobial Resistance*, <http://who.int/mediacentre/factsheets/fs194/en/> (last visited Sept. 26, 2011) (recognizing patient compliance, self-medication, and pressure on providers to take tangible action to address the symptoms of their patients as additional factors contributing to antibiotic resistance).

II. THE ROOTS OF ANTIBIOTIC RESISTANCE

A. The History and Current Status of Antibiotics

The term “antibiotic” was first used as a noun in 1941 by Selmon Walksin to describe a class of molecules that directly antagonized the growth of microorganisms.⁷ While the descriptive term for these molecules did not arise until the 1940s, the search for compounds that could neutralize the effects of infectious microbes dates back to the late nineteenth century.⁸ Early antibiotics, such as pyocyanase and salvarsan, did effectively inhibit the growth of infectious microorganisms, but they were too toxic and unstable to be used as a practical medical treatment.⁹ Alexander Fleming’s chance discovery of penicillin in 1928 represents the first true antibiotic that was effective, reliable, and safe to use in humans.¹⁰ Penicillin first gained worldwide attention when it was used to combat infection in burn victims after the Cocoanut Grove fire of 1942.¹¹ While penicillin would go on to become one of the most successful and influential medical treatments in the history of mankind, Fleming immediately recognized the potential for the development of antibiotic resistance, and cautioned the audience at his Nobel Prize acceptance speech

⁷ See Clardy et al., *supra* note 2.

⁸ Colin Robert Crossman, *Arming Our Enemies: How Parallel Imports Could Increase Antimicrobial Resistance*, 31 N.C.J. INT’L L. & COM. REG. 823, 824 (2006); see Levy, *supra* note 4, at 32.

⁹ Levy, *supra* note 4, at 35–36.

¹⁰ *Id.* at 37–39; see also Alexander Fleming, *Penicillin*, Nobel Lecture (Dec. 11, 1945). This lecture detailed the serendipity of Fleming’s discovery. After returning from vacation, Fleming noticed that one of his Petri dishes had been contaminated by a “mould” that appeared to be destroying the *staphylococci* bacteria also growing on the plate. Levy, *supra* note 4, at 37; see Fleming, *Penicillin*. Further investigation led to the elucidation of penicillin, which he decided to name after the mould from which it was derived; a fungus belonging to the genus *Penicillium*. See Fleming, *Penicillin*.

¹¹ See Levy, *supra* note 4, at 1–7. The Cocoanut Grove was a popular bar in the Boston area that caught fire, killing hundreds, and leaving many survivors horribly burned. *Id.* at 2–4. The burn victims faced the dim reality that their weakened immune systems would be easily overcome by infection, a prognosis that compelled the U.S. government to release a substantial quantity of penicillin to the public for the first time in history. *Id.* at 1–2, 5.

about the dangers of “underdosage.”¹² Fleming observed that underdosage “educate[d] the microbes” to resist the effects of penicillin, leaving those subsequently infected by the surviving resistant microbes unresponsive to the same antibiotics that were once effective in treating the disease.¹³ These observations were remarkably prophetic, as penicillin-resistant strains of bacteria had become widespread by 1949, only seven years after the Cocoanut Grove fire.¹⁴

Today, there are many different classes of antibiotics available to medical practitioners.¹⁵ However, many of the organisms that these antibiotics are designed to treat are quickly developing resistance to drugs in all classes.¹⁶ Perhaps even more troubling is the fact that the development of new antibiotics has ground to a halt as large pharmaceutical companies, once the leaders in antibiotics research and development, have shifted their focus to more profitable and less costly research endeavors.¹⁷ The lack of any viable replacements or alternatives for antibiotics that are no longer effective makes the resurrection of once well-controlled diseases, such as tuberculosis,

¹² Fleming, *supra* note 10, at 93 (“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.”).

¹³ *Id.* (“Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies.”).

¹⁴ Jeremy R. Knowles, *Penicillin Resistance: The Chemistry of β -Lactamase Inhibition*, 18 ACCTS. CHEMICAL RES. 97, 97 (1985), <http://pubs.acs.org/doi/pdf/10.1021/ar00112a001> (“By 1949, more than half of all *Staphylococcus pyogenes* isolates from a U.K. hospital were resistant [to penicillin], and the continued usefulness of this splendid addition to the meager armoury of chemotherapeutics was in doubt.”).

¹⁵ See Karen M. Overbye & John F. Barret, *Antibiotics: Where Did We Go Wrong?*, 10 DRUG DISCOVERY TODAY 45, 46 (2005) (outlining the various classes of antibiotics, such as carbapenems, tetracyclines, and quinolones, and the various stages of development for novel therapeutics in each category).

¹⁶ *Id.* at 46.

¹⁷ *Id.* at 49. The authors address the question, “where did we go wrong?” in the development of antibiotics by noting eight major sources of blame for antibiotic resistance. One source of blame the authors identify is the “under-appreciation of resistance.” The authors note “the treatment of drug-resistant pathogens represents a renewable unmet medical need, but does not yet represent a significant commercial opportunity for industry.”

malaria, dysentery, and bubonic plague, all but inevitable as these diseases rapidly develop resistance to the antibiotics once used to treat them.¹⁸

Several microbes have become particularly prominent in recent years and have garnered substantial media attention, including: methicillin-resistant *Staphylococcus aureus* (“MRSA”)¹⁹, *Streptococcus pneumoniae* (“strep”, “strep pneumo”)²⁰ and extensively drug-resistant tuberculosis (“XDR TB”)^{21,22} MRSA infections on the skin and in the airways are frighteningly common in hospital settings, and the broad spectrum resistance of this organism to almost all classes of antibiotics make it particularly difficult to combat.²³ Cases of MRSA have risen dramatically since 1997.²⁴ Although there is evidence that this increase has stabilized, MRSA still infected an estimated 94,360 people in 2005.²⁵ Approximately 18,650 of these infected individuals died during the hospital stay related to their MRSA infections.²⁶ Similarly, *Streptococcus pneumonia* was once easily treated by

¹⁸ See Ron Gasbarro, *Combating Growing Antibiotic Resistance*, American Druggist, Feb. 1996 at 49 (noting the potential for resurgence of tuberculosis, malaria, and dysentery; all diseases once thought eradicated but now regaining their former potency). See also Michael Misocky, *The Epidemic of Antibiotic Resistance: A Legal Remedy to Eradicate the “Bugs” in the Treatment of Infectious Diseases*, 30 AKRON L. REV. 733, 735 (1997) (“As a result, many horrific diseases, once thought eradicated, have resurrected to impose a significant health threat.”).

¹⁹ Mark C. Enright et al., *The Evolutionary History of Methicillin-Resistant Staphylococcus Aureus (MRSA)*, 99 PROCEEDINGS OF THE NAT’L ACAD. OF SCI. 7687, 7687 (2002).

²⁰ Peter C. Appelbaum, *Antimicrobial Resistance in Streptococcus Pneumoniae: An Overview*, 15 CLINICAL INFECTIOUS DISEASES 77, 77 (1992).

²¹ N. Sarita Shah et al., *Worldwide Emergence of Extensively Drug-resistant Tuberculosis*, 13 EMERGING INFECTIOUS DISEASES 380, 380 (2007).

²² This list is far from exhaustive. Other prominent antibiotic resistant organisms include: Vancomycin-resistant *Enterococcus*, *Klebsiella* species, *Clostridium difficile*, *Pseudomonas aeruginosa*, and *Acinetobacter Baumannii*. See Michael R. Mulvey & Andrew E. Simor, *Antimicrobial Resistance in Hospitals: How Concerned Should We Be?*, 180 CANADIAN MED. ASS’N J. 408, 409 (2009).

²³ See Enright, *supra* note 19, at 7687 (“[MRSA] is a major cause of hospital-acquired infections that are becoming increasingly difficult to combat because of emerging resistance to all current antibiotic classes.”).

²⁴ R. Monina Klevens et al. *Invasive Methicillin-resistant Staphylococcus aureus Infections in the United States*, 298 JAMA 1763, 1763 (2007).

²⁵ *Id.* at 1767.

²⁶ *Id.*

penicillin, but in 1974 medical practitioners throughout the world began reporting that the organism had become completely resistant to penicillin.²⁷ Likewise, XDR TB has emerged in more than ninety countries throughout the world.²⁸ Although a twenty-four month treatment with a highly specialized second-line drug can still combat XDR TB, new evidence shows that the organism is now developing resistance to even this rare and highly specialized treatment.²⁹ These organisms have evolved a frightening invulnerability to mankind's most ingenious treatments.³⁰ Unless something is done to curb the effects of antibiotic resistance, mankind may be facing a global superbug epidemic.³¹

B. Mankind's Role in Antibiotic Resistance

While the details regarding the development and spread of antibiotic resistance are complex and dependent on many different factors, one thing is clear: the perpetuation of antibiotic resistance is accelerated by the excessive use of antibiotics by humans.³² Constant exposure to antibiotics selects those microorganisms best suited to survive treatment, and the natural ability of microorganisms to share genetic information allows for the expansion of resistance until an entire bacterial species becomes resistant to a given antibiotic.³³ By

²⁷ See Appelbaum, *supra* note 20, at 81 ("Resistance to penicillin among strains of *S. Pneumoniae* is now widespread and is rapidly increasing all over the world.").

²⁸ See Shah, *supra* note 21.

²⁹ See *id.* (noting that XDR TB is exhibiting "such extensive drug resistance as to be nearly untreatable with currently available drugs").

³⁰ See Misocky, *supra* note 18, at 735 ("The evolution of antibiotics resistance ... mandates heightened concern for a plausible 'superbug' epidemic") (citing Levy *supra* note 4, at 97, "It is the multiply resistant bacteria appearing in different diseases and ecological setting that truly threaten our ability to treat infections successfully today.").

³¹ *Id.*

³² See Smith & Coast, *supra* note 2, at 135 ("Although the development and spread of resistance is a complex process that depends on many factors, genetic transformation of microorganisms into resistant strains is accelerated by the use of antibiotics.").

³³ See Fernando Bacquero & Jesus Blazquez, *Evolution of Antibiotic Resistance*, 12 TRENDS IN ECOLOGY & EVOLUTION 482, 482 (1997) ("A huge environmental antibiotic pressure, resulting from industrial production and marketing of these drugs, has simultaneously contributed to the increase in the diversity of resistant phenotypes, to the selection of the fittest among them, and to the dispersal of resistant genes, which is expected to result in a

understanding the ways in which humans misuse antibiotics and the settings in which these abuses occur, we can more effectively combat these root causes of antibiotic resistance.

Humans misuse antibiotics in three significant settings: the medical setting, the antibacterial hygiene product setting, and the veterinary or food animal production setting.³⁴

In the medical setting, behaviors of both the patient and the physician contribute to antibiotic resistance.³⁵ Many patients unknowingly contribute to antibiotic resistance by insisting on receiving the newest and most expensive antibiotic treatments available.³⁶ By pressuring their healthcare providers into prescribing the newest antibiotic treatment, patients are exposing infectious microbes to new classes of antibiotic and encouraging the selection of organisms resistant to these rare and valuable treatments.³⁷ The overuse of these drugs makes them less and less effective over time.³⁸ A more common mistake made by patients is to stop taking antibiotics before completion of the course of treatment prescribed by the physician.³⁹ By failing to complete the entire course of treatment, patients do not completely eradicate the infection from their bodies.⁴⁰ Instead, the microbes that are most resistant to the antibiotic being used remain viable and multiply, creating a new and more resistant

significant acceleration of the rate of microbial evolution.”).

³⁴ See World Health Org., *supra* note 5.

³⁵ *Id.* See also Centers for Disease Control and Prevention, *supra* note 3.

³⁶ See World Health Org., Antimicrobial Resistance, <https://apps.who.int/inf-fs/en/fact194.html> (last visited Oct. 5, 2011) (“For example, many patients believe that new and expensive medications are more efficacious than older agents. In addition to causing unnecessary health care expenditure, this perception encourages the selection of resistance to these newer agents as well as to older agents in their class.”).

³⁷ *Id.*

³⁸ *Id.*

³⁹ See Centers for Disease Control and Prevention, Antibiotic Resistance Questions & Answers, <http://www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html> (last visited Oct. 7, 2011) (recommending that patients “[t]ake an antibiotic exactly as the healthcare provider tells you. Do not skip doses. Complete the prescribed course of treatment even if you are feeling better. If treatment stops too soon, some bacteria may survive and re-infect.”).

⁴⁰ *Id.*

bacterial colony that can be transmitted to the next potential host.⁴¹ Patients often save antibiotics that should be taken as part of a complete treatment regimen for possible future infections, and this behavior effectively doubles the selective pressure exerted on the infectious microbes to acquire resistance.⁴² Patients also appear to urge physicians to prescribe antibiotics even when most symptoms seem to indicate that the patient is suffering from a malady that antibiotics cannot treat.⁴³ Unfortunately, physicians appear to be acquiescing to their patients' demands in order to deliver a positive treatment outcome and retain the patients' business.⁴⁴ In fact, patients appear willing to go to great lengths to obtain prescriptions for antibiotics, including exaggerating symptoms, even when the drugs are completely unnecessary.⁴⁵

While the intricacies of the physician-patient relationship's effect on antibiotic resistance have been studied in depth, the effect of antibacterial hygiene products on antibiotic resistance is poorly understood and controversial.⁴⁶ There is evidence that a link exists

⁴¹ *Id.* See also World Health Organization, *supra* note 5, at "Factors That Encourage the Spread of Resistance" ("Patients forget to take medication, interrupt their treatment when they begin to feel better, or may be unable to afford a full course, thereby creating an ideal environment for microbes to adapt rather than be killed.").

⁴² See Centers for Disease Control and Prevention, *supra* note 3 (recommending that patients "[d]o not save some of [their] antibiotic for the next time [they] get sick" and urging patients to "[d]iscard any leftover medication once [they] have completed [their] prescribed course of treatment."). See also Jean Claude Pechere, *Patients' Interviews and Misuse of Antibiotics*, 33 CLINICAL INFECTIOUS DISEASES S170, S170 (2001) (observing that of the 5,379 patients interviewed, "[a]bout 1 patient in 4 saved part of the antibiotic course for future use. Sixty-nine percent ... claimed to have taken the course until the end.").

⁴³ See World Health Organization, *supra* note 5 ("Physicians can be pressured by patient expectations to prescribe antimicrobials even in the absence of appropriate indications... Prescribing 'just to be on the safe side' increases when there is diagnostic uncertainty, lack of prescriber knowledge regarding optimal diagnostic approaches, lack of opportunity for patient follow-up, or fear of possible litigation.").

⁴⁴ See *id.*

⁴⁵ See Pechere, *supra* note 42, at S171 (observing that of the 5,379 patients surveyed "11% of [them] . . . had to exaggerate [their] symptoms to get [an antibiotic prescription] from their physician.") The article goes on to posit that this urge to obtain a prescription for antibiotics could be a reflection of the patients' feeling that they are "a better judge than their doctor" or the perception of antibiotics as "strong, efficient drugs" that will make them feel better. *Id.* at S171.

⁴⁶ See Centers for Disease Control and Prevention, *supra* note 5 ("More studies examining

between antibacterial chemicals found in household cleaners or soaps and the development of resistance in microorganisms; however, the human health consequences of these interactions are unclear.⁴⁷ Interestingly, the Food and Drug Administration concluded in 2005 that products containing antibacterial agents are no more effective at infection control than those products that do not contain antibacterial agents.⁴⁸ This begs the question: if the potential of antibacterial agents to contribute to antibiotic resistance exists, and the addition of antibacterial agents to hygiene products has no significant effect on infection control, why is the addition of antibacterial agents to hygiene products permitted at all? The debate over antibacterial hygiene products and their relationship to antibiotic resistance appears to be just beginning.

Another significant area of human contribution to antibiotic resistance is the overuse of antibiotics in animals raised for food.⁴⁹ The use of antibiotics in animal feed to promote the healthy growth of animals raised for food began in the late 1950's without any investigation as to the potential consequences of the addition.⁵⁰ The observation that those animals whose feed was treated with antibiotics grew larger than those without antibiotics, also known as the "antibiotic growth effect," has never been fully explained, and

resistance issues related to these products are needed.").

⁴⁷ See *id.* ("Although a link between antibacterial chemicals used in personal cleaning products and bacterial resistance has been shown in vitro studies [in a controlled environment], no human health consequence has been demonstrated."). But see Allison E. Aiello & Elaine Larson, *Antibacterial Cleaning and Hygiene Products as an Emerging Risk Factor for Antibiotic Resistance in the Community*, 3 LANCET INFECTIOUS DISEASES 501, 501 (2003) ("[W]hen bacteria are exposed to triclosan in vitro, mechanisms can be elicited that can confer resistance to antibiotics used to treat human disease.").

⁴⁸ See Centers for Disease Control and Prevention, *supra* note 5 ("The Food and Drug Administration [FDA] Nonprescription Drugs Advisory Committee voted unanimously on October 20, 2005 that there was a lack of evidence supporting the benefit of consumer products including handwashes, bodywashes, etc., containing antibacterial additives over similar products not containing antibacterial additives.").

⁴⁹ See Briceno, *supra* note 4, at 523 (citing World Health Organization, *supra* note 5, at "Executive Summary").

⁵⁰ See Jay P. Graham et al., *Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis*, 122 PUB. HEALTH REPORTS 79, 80 (2007) ("The use of antibiotics to enhance growth and feed efficiency and reduce mortality in broiler production was introduced without rigorous testing as to efficacy some 50 years ago.").

few published studies have investigated the legitimacy of these observations.⁵¹ Despite the tenuous nature of the antibiotic growth effect's scientific rationale, the vast majority of livestock antibiotics are administered for non-therapeutic purposes, such as enhanced growth and the prevention of disease.⁵² Unlike therapeutic doses that treat an animal in response to infection for a given period of time, non-therapeutic doses of antibiotics, such as those administered as antibiotic growth promoters, treat a large amount of animals at one time as a preventative measure designed to reduce costs.⁵³ This indiscriminate dosing results in the ingestion of sub-optimal doses of antibiotics by food animals, making them the perfect incubators for antibiotic-resistant infections.⁵⁴ These resistant organisms are then passed to humans when the animals are slaughtered and eaten.⁵⁵

In short, antibiotic resistance is a problem that is directly exacerbated by human actions. In order to combat antibiotic resistance, humans must find ways to reduce the chronic misuse and overuse of antibiotics.

III. THE LEGAL SOLUTIONS TO ANTIBIOTIC RESISTANCE

The problem of antibiotic resistance has not been ignored, but a truly comprehensive solution to the problem has yet to emerge.⁵⁶ This is partly due to the numerous and complex root causes of antibiotic resistance.⁵⁷ Despite these difficulties, antibiotic resistance

⁵¹ While it has been hypothesized that the antibiotic growth effect is caused by the reduction of pathogenic bacteria in the intestinal tract of the animal, this hypothesis has never been verified, and the efficacy of adding antibiotics to animal feed remains an open question. *See id.* at 80.

⁵² *See* Briceno, *supra* note 4, at 523 (quoting Karen Florini & Rebecca J. Goldberg, *Playing Chicken With Antibiotics*, 22 ENV'T'L FORUM 22, 22 (2005)).

⁵³ *See* Graham et al., *supra* note 50, at 80.

⁵⁴ *See id.*

⁵⁵ *See id.*

⁵⁶ *See* Richard S. Saver, *In Tepid Defense of Population Health: Physicians and Antibiotic Resistance*, 34 AM. J. L. & MED. 431, 433 (2008) ("Effective strategies for combating antibiotic resistance unfortunately remain elusive.").

⁵⁷ *Id.* (listing examples of these root causes, such as "weak surveillance for resistance; aggressive promotion of antibiotics by pharmaceutical companies; lax infection control

must be more effectively addressed if humans are to maintain dominion over microorganisms and prevent superbug epidemics from devastating the globe. This section discusses four possible legal solutions to the problem of antibiotic resistance: 1) intellectual property strategies and the use of patents to provide economic incentives for pharmaceutical companies to develop novel antibiotics; 2) legislative strategies that impose statutory guidelines on antibiotic usage in medical, hygiene, and veterinary settings; 3) tort remedies, such as punitive damages, as a means of curbing the persistent misuse and overuse of antibiotics; and 4) FDA regulation using a Risk Evaluation and Mitigation Strategy (“REMS”) to restrict the use of antibiotics in both humans and animals.

A. Intellectual Property Strategies

A major problem in the battle against antibiotic resistance is the lack of novel antibiotics to replace those that no longer effectively treat organisms that have developed resistance to other antibiotic treatments.⁵⁸ In fact, a 2004 survey of fifteen major pharmaceutical companies, including Merck, Pfizer, and Johnson & Johnson, revealed that out of the 506 drugs in the research and development pipeline at that time, only five were antibiotics.⁵⁹ The major cause of this decline in antibiotic development is the poor return on investment pharmaceutical companies experience when producing new antibiotics.⁶⁰ One reason antibiotics have a lower rate of return

practices; patients' irrational demand for antibiotics even when they may not be effective; unwarranted clinical variation in the way physicians prescribe and monitor antibiotics; inappropriate patterns of antibiotic use in agriculture and food-animal products that may impact human health; and a possible downturn in discovery and commercial development of antibiotics.”).

⁵⁸ See Overbye & Barrett, *supra* note 15, at 51. See also Brad Spellberg et al., *The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America*, 46 *CLINICAL INFECTIOUS DISEASES* 155 (2008) available at www.idsociety.org/workarea/downloadasset.aspx?id=9048 (acknowledging the “alarming decline...in the research and development of new antibiotics” to deal with the threat of antibiotic resistance).

⁵⁹ See *INFECTIOUS DISEASES SOCIETY OF AM., BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES, A PUBLIC HEALTH CRISIS BREWS* 14 (2004). The study goes on to note that only 10 new antibiotics have been approved by the FDA since 1998. *Id.* at 15.

⁶⁰ Spellberg et al., *supra* note 58, at 158 (“The cause of the decline in antibiotic development is

on investment is the fact that they are short-term therapies that completely cure their target disease.⁶¹ Additionally, developing novel antibiotics is extremely costly, both in terms of investment in drug discovery and the funding required for regulatory approval.⁶² Furthermore, appropriately limiting the use of novel antibiotics in order to prevent antibiotic resistance produces a strong disincentive for companies to invest in the development of these drugs because their use will be discouraged, and their profitability will be decreased.⁶³

While these obstacles are certainly daunting, commentators have suggested ways in which intellectual property law can provide a means for pharmaceutical companies to recoup their investment in novel antibiotic development. These “supply side” approaches propose significant changes to patent system incentives in order to encourage pharmaceutical companies to invest in novel antibiotic therapies.⁶⁴

For example, the Infectious Diseases Society of America (“IDSA”) has strongly advocated the extension of patent periods for novel antibiotics to allow pharmaceutical companies to enjoy market exclusivity for significantly longer periods of time.⁶⁵ Proponents of extended patent periods for antibiotics argue that, in addition to allowing more time for pharmaceutical companies to generate profits and recoup investment, a longer period of monopoly will encourage pharmaceutical companies to reserve antibiotics for future public health threats when the highest possible prices can be obtained.⁶⁶ Thus, while pharmaceutical companies are more likely to invest in

multi-factorial, but fundamentally, each factor relates to return on investment.”).

⁶¹ *Id.* (“Ironically, antibiotics are victims of their own success; they are less desirable to drug companies and venture capitalists because they are more successful than other drugs.”)

⁶² *See id.* (citing Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 JOURNAL OF HEALTH ECON. 151 (2003)).

⁶³ Spellberg et al., *supra* note 58, at 158.

⁶⁴ Saver, *supra* note 56, at 444.

⁶⁵ *Id.* *See also* INFECTIOUS DISEASES SOC’Y OF AM., *supra* note 59, at 22.

⁶⁶ Eric Kades, *Preserving a Precious Resource: Rationalizing the Use of Antibiotics*, 99 NW. L. REV. 671, 672 (2005). *See also* Saver, *supra* note 48, at 444 (“[A] longer period of time-limited monopoly will encourage pharmaceutical companies to postpone sales and reserve drugs for future public health threats, when even higher prices can be obtained.”).

the development of potentially profitable and novel antibiotics, the drugs they develop are less likely to be misused and the development of resistance can be diminished.⁶⁷

Another related approach is the “wild card” patent extension reform.⁶⁸ Under this approach, pharmaceutical companies that receive FDA approval for “high priority” antibiotics would be allowed to extend the market exclusivity time for one of their other drugs.⁶⁹ This extension would allow pharmaceutical companies to reap windfalls from more profitable drugs that could make investment in novel antibiotic research and development more feasible.⁷⁰

While these strategies have attracted significant political, legislative, and academic interest,⁷¹ there are problems with the “supply side” approaches.⁷² For one, even with longer patent periods, it may be unrealistic to expect that pharmaceutical companies, driven by short-term gains, would be willing to delay aggressive promotion of their newest antibiotics.⁷³ Additionally, nothing guarantees that biological innovation is capable of producing new and effective antibiotics, no matter the incentive structure.⁷⁴ These reforms also do almost nothing to address the chronic misuse

⁶⁷ Kades, *supra* note 66, at 672; Saver, *supra* note 56, at 444.

⁶⁸ INFECTIOUS DISEASES SOC'Y OF AM., *supra* note 59, at 22; Saver, *supra* note 56, at 444.

⁶⁹ Saver, *supra* note 56, at 444.

⁷⁰ *Id.*

⁷¹ See S. 975, 109th Cong. § 202 (2005) (proposing an addition to Title III of the Public Service Act, 42 U.S.C. § 243, that would allow counter-measures to “biological and chemical agents, toxins, and nuclear and radiological materials that may be used as weapons of mass destruction or that are infectious diseases,” such as antibiotics, to be eligible for patent term extension). See also Jessica P. Schulman, *Patents and Public Health: The Problems With Using Patent Law Proposals to Combat Antibiotic Resistance*, 59 DEPAUL L. REV. 221, 222–23 (2009); Saver, *supra* note 56, at 444 (citing the Protecting America in the War on Terror Act of 2005, S.3, 109th Cong. (2005); the Biological, Chemical, and Radiological Weapons Countermeasures Research Act (BioShield II), S.666, 108th Cong. (2003)).

⁷² Saver, *supra* note 56, at 444 (“Pragmatic considerations suggest that this current enthusiasm for such supply side approaches should be tempered.”).

⁷³ *Id.*

⁷⁴ *Id.* at 445.

and overuse of antibiotics already off patent.⁷⁵ The existing inappropriate use of antibiotics that supply side reforms ignore can lead to the phenomenon of cross-resistance, where an organism becomes resistant to an entire class of antibiotics.⁷⁶ This phenomenon further limits the ability of pharmaceutical companies to innovate quickly enough to keep pace with the rapid development of antibiotic resistance.⁷⁷ Indeed, the very nature of a patent is poorly suited for use in antibiotics because, unlike other inventions, the inventor's incentive to exploit the invention while it is protected by the patent diminishes its usefulness.⁷⁸

In short, while intellectual property strategies seem at first blush to present a valid solution, they only affect a small portion of the overall antibiotic resistance problem and may be unrealistic to effectively implement.

B. Legislative Strategies

Another method for combating antibiotic resistance could come from the legislative branch of the federal government. While Congress has not ignored the problem of antibiotic resistance, it has yet to take decisive action to address the problem in a comprehensive manner.

Congress first tackled antibiotic resistance in 1995 when the Congressional Office of Technology Assessment issued the "Impacts of Antibiotic Resistant Bacteria" report.⁷⁹ In 1999, the General

⁷⁵ *Id.*

⁷⁶ *Id.* ("Even if revised patent rights encourage a pharmaceutical company to reserve a perceived blockbuster drug and not rush to market it aggressively, inappropriate use of another antibiotic already on the market within the same therapeutic class may nonetheless create resistance problems for the new drug as well.")

⁷⁷ *Id.*

⁷⁸ Schulman, *supra* note 71, at 223 ("Generally, the inherent usefulness of an invention is not altered by an inventor's incentive to exploit the value of the invention while it is being protected by the patent.")

⁷⁹ U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, IMPACTS OF ANTIBIOTIC-RESISTANT BACTERIA, OTA-H-6298 (Washington, DC: U.S. Government Printing Office, September 1995) ("The impacts of antibiotic-resistant bacteria can be reduced by preserving the effectiveness of current antibiotics through infection control, vaccination and prudent use of antibiotics, and by developing new antibiotics specifically to treat infections caused by

Accounting Office (“GAO”) issued another report to Congress recognizing the emergence, spread, and potential threat that antibiotic resistance posed worldwide.⁸⁰ In 2000, the Public Health Threats and Emergencies Act was introduced in the House of Representatives.⁸¹ This bill sought to establish an Antimicrobial Resistance Task Force to coordinate federal programs in combating antibiotic resistance and provided grants to raise awareness about the problem.⁸² In late 2001, a group of Energy and Commerce Committee members introduced the Antibiotic Resistance Prevention Act, which sought to provide funding for antibiotic resistance awareness and research.⁸³ While neither of these bills became law, they did indicate that members of Congress were aware of the problem of antibiotic resistance at the turn of the millennium, and that some were trying actively to address the issue.

In September 2007, the Strategies to Address Antimicrobial Resistance Act (“STAAR Act”) was first introduced by Representatives Matheson (D-UT) and Ferguson (R-NJ).⁸⁴ The bill sought to combat antibiotic resistance by funding data compilation and awareness programs.⁸⁵ Despite vigorous endorsement from scientific organizations, such as the Infectious Diseases Society of America, the Union of Concerned Scientists, and the American Public

antibiotic resistant bacteria.”).

⁸⁰ U.S. GEN. ACCOUNTING OFFICE, ANTIMICROBIAL RESISTANCE: DATA TO ASSESS PUBLIC HEALTH THREAT FROM RESISTANT BACTERIA ARE LIMITED (1999), available at <http://www.gao.gov/archive/1999/hx99132.pdf>.

⁸¹ Public Health Threats and Emergencies Act, S. 2731/H.R. 4964, 106th Cong. (1999). Parts of this bill did become law and would form the foundation of the Strategies to Address Antimicrobial Resistance (“STAAR”) legislation. See also Infectious Diseases Society of America, Highlights of Past U.S. Response to Antimicrobial Resistance, http://www.idsociety.org/uploadedFiles/idsa/policy_and_advocacy/current_topics_and_issues/antimicrobial_resistance/strengthening_us_efforts/staar_act/history%20of%20Congressional%20response%20060910.pdf (last visited Oct. 6, 2011).

⁸² See Infectious Disease Society of America, *supra* note 81, at 2.

⁸³ Antibiotic Resistance Prevention Act, H.R. 1771, 107th Cong. (2001). See also Infectious Disease Society of America, *supra* note 81, at 2.

⁸⁴ The Strategies to Address Antimicrobial Resistance Act, H.R. 3697, 110th Cong. (2007).

⁸⁵ See Infectious Diseases Society of America, STAAR Act Highlights, <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=14468> (last visited Feb. 27, 2011).

Health Association, the bill has not been passed into law and its re-introductions have also proven to be futile.⁸⁶ In 2009, Representative Slaughter (D-NY) introduced the Preservation of Antibiotics for Medical Treatment Act (PAMTA) in the House of Representatives.⁸⁷ This act proposed drastic action to address the problem of antibiotic resistance, including elimination of the use of subtherapeutic doses of antibiotics in livestock feed and the imposition of tough approval standards for new antibiotics to be used in animals.⁸⁸ While the legislation has enjoyed overwhelming support from over 300 scientific organizations, it has not been signed into law.⁸⁹

Although Congress has failed to pass legislation specifically geared toward combating antibiotic resistance, it has managed to increase funding for antibiotic research in legislation targeting other matters.⁹⁰ It has also passed legislation that could be used to combat antibiotic resistance, though it was not intended to do so.⁹¹ However, these tangential remedies are not sufficient to impact a problem as widespread and potentially devastating as antibiotic resistance. Unfortunately, Congress appears reluctant to tackle the issue head-on, perhaps because of a strong lobbying presence from agribusiness

⁸⁶ Infectious Diseases Society of America, Organizations Endorsing the STAAR Act, <http://www.idsociety.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=15947> (last visited Feb. 27, 2011); *see also* Strategies to Address Antimicrobial Resistance Act, S. 2313, 110th Cong. (2007); Strategies to Address Antimicrobial Resistance Act, H.R. 2400, 111th Cong. (2009).

⁸⁷ Preservation of Antibiotics for Medical Treatment Act, H.R. 1549, 111th Cong. (2009).

⁸⁸ Representative Louise Slaughter, PAMTA, http://www.louise.house.gov/index.php?option=com_content&view=article&id=1315&Itemid=138#organizations (last visited Feb. 27, 2011).

⁸⁹ *Id.*

⁹⁰ *See* Pandemic and All-Hazards Preparedness Act, Pub. L. No. 109-417, 120 Stat. 2831 (2006) (including “naturally occurring diseases” as a hazard for which research and preparedness funding would be granted); *see also* Infectious Disease Society of America, *supra* note 81, at 2.

⁹¹ *See* Drug Price Competition and Patent Term Restoration, Pub. L. No. 98-417, 98 Stat. 1585, 1600-01 (1984) (altering the market exclusivity terms awarded to generic antibiotics); Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2051 (1983) (granting seven years of market exclusivity to drugs developed in response to rare diseases, an incentive which could be extended to novel antibiotic therapies).

interests that depend on antibiotic use as a method of cost control.⁹² Experts have identified pharmaceutical and agribusiness lobby groups as the primary reason why comprehensive antibiotic resistance legislation, such as PAMTA, has been repeatedly abandoned by lawmakers.⁹³ As long as these powerful lobby groups continue to exert pressure on Congress, it is unlikely that comprehensive legislation attacking antibiotic resistance will ever become a reality.

In short, despite the willingness of some members of Congress to address antibiotic resistance and the existence of proposed legislation that experts feel could make a difference, Congress has not and likely will not take the drastic action most experts feel is necessary to combat antibiotic resistance.

C. Tort Remedies

Tort remedies, such as punitive damages, could be used as a mechanism to deter the behaviors that contribute to antibiotic resistance. Proponents of the use of punitive damages as a method of influencing behavior argue that punitive damages serve two primary purposes.⁹⁴ First, punitive damages punish past wrongful conduct.⁹⁵ Second, punitive damages deter future wrongful conduct.⁹⁶ In determining whether punitive damages are appropriate, most jurisdictions require more than mere negligence.⁹⁷ Courts often require “a conscious and deliberate disregard of the interests of

⁹² Kammerle Schneider & Laurie Garrett, *Non-therapeutic Use of Antibiotics in Animal Agriculture, Corresponding Resistance Rates, and What Can be Done About It*, Center for Global Development, <http://www.cgdev.org/content/general/detail/1422307/> (last visited Feb. 27, 2011) (quoting Representative Slaughter as saying, “[w]e’re up against a pretty strong lobby. It will come down to whether members of Congress want to protect their constituents or agribusiness.”).

⁹³ *Id.*

⁹⁴ Griffin B. Bell & Perry E. Pierce, *Punitive Damages and the Tort System*, 22 U. RICH. L. REV. 1, 4 (1987).

⁹⁵ *Id.*

⁹⁶ *Id.*

⁹⁷ *Id.* at 10.

others.”⁹⁸ Some courts use an expanded gross negligence standard that includes “conscious indifference to consequences” as a justification for awarding punitive damages.⁹⁹ Punitive damages are awarded in a variety of different types of actions, including personal injury claims and mass tort claims.¹⁰⁰

In the case of antibiotic resistance, the wrongful conduct to be deterred is the chronic misuse and overuse of antibiotics in both humans and livestock. Both physicians who inappropriately prescribe antibiotics to patients and industrial food producers that use sub-therapeutic doses of antibiotics in livestock feed could be argued to be consciously indifferent to the consequences of their actions.¹⁰¹ Thus, should a plaintiff bring a personal injury or mass tort claim against a physician or industrial food producer seeking compensation for injury caused by an antibiotic resistant infection that could be traced to the conduct of the defendant, a court could award punitive damages as a method of deterring the defendants from engaging in the behaviors that contributed to the creation and perpetuation of antibiotic resistant organisms.

While the use of punitive damages as a deterrent is compatible with the goal of deterring the inappropriate use of antibiotics, there are major problems with this approach.¹⁰² First, the traditional negligence tort law norms of duty, breach, causation, and damages may be insurmountable obstacles for plaintiffs attempting to sue physicians or industrial farm animal producers.¹⁰³ Physicians

⁹⁸ *Id.* at 9.

⁹⁹ *Id.* at 10.

¹⁰⁰ *Id.* at 11-14. See also Gary T. Schwartz, *Mass Torts and Punitive Damages, a Comment*, 39 VILL. L. REV. 415, 415 (discussing the use of punitive damages in mass tort cases).

¹⁰¹ See THE PEW COMMISSION ON INDUSTRIAL FARM ANIMAL PRODUCTION, PUTTING MEAT ON THE TABLE: INDUSTRIAL FARM ANIMAL PRODUCTION IN AMERICA, EXECUTIVE SUMMARY 5-8 (2008) available at http://www.ncifap.org/_images/PCIFAPSmry.pdf (noting that industrial farm animal producers are aware that sub-optimal doses of antibiotic contribute to antibiotic resistance but still rely on the practice as a means of reducing costs). See also World Health Organization, *supra* note 5.

¹⁰² These problems are in addition to the extremely controversial nature of punitive damages in general. See Bell & Pierce, *supra* note 94, at 4-9 (arguing that punitive damages are so inconsistently used and incompatible with justice that their use should be completely abandoned or drastically reformed).

¹⁰³ Scott B. Markow, *Penetrating the walls of Drug-Resistant Bacteria: A Statutory Prescription to*

probably do not owe a duty to the population as a whole or even a class of potential victims not to misuse antibiotics on an individual patient.¹⁰⁴ On the contrary, physicians owe a duty to their patients to treat and cure bacterial infections.¹⁰⁵ As one commentator has pointed out, “[b]ecause any use of antibiotics will lead to some development of resistance, if practitioners had a duty to the population to never induce resistance, they could never prescribe antibiotics to patients, even for a legitimate use.”¹⁰⁶ Courts are unlikely to create such a paradox by imposing a duty on a physician not to misuse antibiotics on individual patients.¹⁰⁷ In the case of industrial farm animal production, imposing a duty on producers not to misuse antibiotics in order to protect the consumer may be more realistic, but it is still a stretch from the traditional common law duties recognized in most jurisdictions.¹⁰⁸

Even if a duty not to misuse antibiotics were to be recognized in either context, it would be very difficult for any plaintiff to prove that, but for the defendant’s misuse of antibiotics, they would not have been infected by an antibiotic resistant organism.¹⁰⁹ It would be equally difficult for potential plaintiffs to prove that the misuse of antibiotics by the defendant was a proximate cause of the plaintiff’s

Combat Antibiotic Misuse, 87 GEO. L. J. 531, 543 (1998-1999).

¹⁰⁴ *Id.*; see also PATRICIA M. DANZON, *MEDICAL MALPRACTICE* 139-40 (1985) (pointing out that the standard of care for a physician is determined by custom in the industry of medicine).

¹⁰⁵ Markow, *supra* note 103, at 543. See also *Hellwig v. Potluri*, No. 90-C-55, 1991 WL 285712, at 1 (Ohio Ct. App. Dec. 27, 1991) (holding that a physician had a duty to prescribe antibiotics to a patient who had stepped on a rusty nail.)

¹⁰⁶ Markow, *supra* note 103, at 543.

¹⁰⁷ *Id.*

¹⁰⁸ See *id.* (“[I]t is unlikely that common law would recognize a duty...not to misuse antibiotics.”). But see Schwartz, Goldberg, & Appel, *Can Governments Impose A New Tort Duty To Prevent External Risks? The “No-Fault” Theories Behind Today’s High-Stakes Government Recoupment Suits*, 44 WAKE FOREST L. REV. 923, 924 (2009) (arguing that a current trend in tort law is to hold manufacturers accountable for external costs their products create, even if they are not at fault. Such a rationale could be used in the context of misuse of antibiotics to justify imposing a duty on industrial farm animal producers.).

¹⁰⁹ See Markow, *supra* note 103, at 543-44 (“Since some strains of resistant bacteria existed in nature before antibiotics were ever used, it would be difficult to prove that, but for the misuse of antibiotics, the resistant infection would have emerged.”).

injury.¹¹⁰ As a result, a plaintiff is unlikely to succeed in bringing a negligence action against a physician or industrial farm animal producer for misuse of antibiotics because of the difficulties in proving duty, breach, causation, and damages.

The second major problem with a negligence suit seeking punitive damages against physicians or food animal producers is the prospect that any such lawsuit may be pre-empted by federal law.¹¹¹ Under the Supremacy Clause, state law claims can be pre-empted explicitly, implicitly, or when compliance with both federal and state law is impossible.¹¹² Congress can implicitly pre-empt state law “when it is clear, despite the absence of explicit pre-emptive language, that Congress has intended, by legislating comprehensively, to occupy an entire field of regulation and has thereby left no room for the State to supplement federal law.”¹¹³ Pre-emption would be a viable affirmative defense for industrial farm animal producers because “[m]edicated animal feeds and drugs used in treating animals which are raised for human consumption are also controlled by the FDCA as part of its comprehensive scheme to protect the public from drugs that may be unsafe or ineffective for their intended uses.”¹¹⁴ However, claims against physicians for misuse of antibiotics may not necessarily be pre-empted by federal law.¹¹⁵

¹¹⁰ This depends on the causation standard to be applied. Under the *Polemis* test, there must be a direct link between the event and the injury. In the case of antibiotic resistant infection, several intervening causes could supersede the actions of physicians and industrial farm animal producers and break the chain of causation because it is nearly impossible to determine the source of bacterial infection. The *Wagon Mound* foreseeability test is more friendly to plaintiffs in this situation. Under this test, the defendant must have foreseen the particular type of harm, but not the specific victim, mechanism, or severity of injury. See Markow, *supra* note 103, at 544–45.

¹¹¹ See *Animal Legal Def. Fund Boston, Inc. v. Provimi Veal Corp.*, 626 F.Supp 278, 282 (D. Mass. 1986).

¹¹² *Id.*

¹¹³ *Id.* (quoting *Capital Cities Cable, Inc. v. Crisp*, 467 U.S. 691 (1984)).

¹¹⁴ *Id.* at 282–3.

¹¹⁵ See *Wyeth v. Levine*, 555 U.S. 555 (2009) (holding federal regulatory approval does not shield a pharmaceutical manufacturer from liability under state law, and indicating that in fields of law the state has traditionally occupied, the Court starts with the assumption that the police powers of the state are not pre-empted absent the manifest intentions of

While awarding punitive damages may seem like an effective way to curb antibiotic resistance, closer inspection reveals that tort law is poorly suited to combat the problem. Another strategy is necessary to more adequately address antibiotic resistance in the future.

D. FDA Regulation: A Novel Regulatory Approach

The approach to combating antibiotic resistance that shows the most promise is top-down regulatory reform starting with the Food and Drug Administration (“FDA”). The FDA has been widely criticized for its lack of response to the problem of antibiotic resistance.¹¹⁶ In response to this criticism, the FDA has recently taken a much tougher approach to antibiotic resistance and has at its disposal two novel methods to combat the problem.¹¹⁷ This section will first discuss how the Administrative Procedure Act (“APA”) can be used to compel the FDA to ban the use of sub-therapeutic doses of antibiotics in livestock feed.¹¹⁸ It will then discuss how the FDA can use its expanded statutory authority under the Food and Drug Administration Amendments Act of 2007 (“FDAAA”) to impose a Risk Evaluation and Mitigation Strategy (“REMS”) as a means of combating the inappropriate use of antibiotics by physicians.¹¹⁹

Congress. This decision makes federal pre-emption less likely in areas where state law has traditionally governed, such as in determining the appropriate standard of medical care in prescribing antibiotics).

¹¹⁶ See Arielle Lessing, *Killing Us Softly: How Sub-Therapeutic Dosing of Livestock Causes Drug-Resistant Bacteria in Humans*, 37 B.C. ENVTL. AFF. L. REV. 463, 463 (2010) (“[T]he Food and Drug Administration (FDA) has stood by while antibiotic-resistance in human bacteria has exploded into a critical public health issue.”).

¹¹⁷ See James Andrews, *Flood of Comments to FDA on Antibiotics Draft*, FOOD SAFETY NEWS, Feb. 25, 2011, <http://www.foodsafetynews.com/2011/02/many-react-to-fda-draft-guidance-on-antibiotics/> (discussing the huge response to a draft of new guidelines proposed by the FDA in late 2010 to regulate the use of antibiotics in livestock feed).

¹¹⁸ Lessing, *supra* note 116.

¹¹⁹ Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 511–12 (2010).

1. *The Administrative Procedure Act*

Should the FDA continue to lag behind the rest of the world in effectively responding to the problem of antibiotic resistance, concerned citizens and scientists could use the APA to petition the FDA to withdraw the approval of antibiotics used in livestock feed.¹²⁰ Agency action or inaction is subject to judicial review through the APA, which mandates that government agencies must allow for a system of petition, repeal, modification, or creation of agency rules.¹²¹ The FDA complies with this mandate through a “citizen petition” process by which concerned parties can ask the FDA to issue, change, or cancel a regulation, or to take other action.¹²² Under the program, the FDA can take more than a year to decide whether or not to grant a petition, but it must furnish some form of response to the petitioner.¹²³ Once the FDA makes a decision pursuant to the petition, that decision is reviewable under the APA.¹²⁴

This process affords concerned scientists, public officials, and citizens the opportunity to compel the FDA to do what no governmental body in the United States seems willing to do but what most experts agree is necessary to most effectively combat antibiotic resistance: ban the use of sub-therapeutic doses of antibiotics in livestock feed.¹²⁵ The FDA has the authority to accomplish this goal by withdrawing its approval of the antibiotics used in livestock feed, thus making any addition of these antibiotics to livestock feed illegal.¹²⁶ Should the FDA deny the petition arguing such action, the

¹²⁰ Lessing, *supra* note 116, at 482; *see also* THE DANISH INTEGRATED ANTIMICROBIAL RESISTANCE MONITORING AND RESEARCH PROGRAMME, <http://www.danmap.org> (last visited Feb. 27, 2011).

¹²¹ Lessing, *supra* note 116, at 482. *See* Administrative Procedure Act § 4(d), 5 U.S.C. § 553(e) (2006).

¹²² 21 C.F.R. § 10.30 (2010); U.S. FOOD & DRUG ADMIN., Comment on Regulations, <http://www.fda.gov/aboutfda/contactfda/commentonregulations/default.htm> (last visited Feb. 27, 2011).

¹²³ Lessing, *supra* note 116, at 482.

¹²⁴ *Id.* at 483; *see* 5 U.S.C. § 704 (2006).

¹²⁵ Lessing, *supra* note 116, at 487; *see also supra* text accompanying notes 49-55.

¹²⁶ Lessing, *supra* note 116, at 487.

judicial review process mandated by the APA gives the challenging party the opportunity to use the vast amount of persuasive data to argue that such action is indeed necessary to prevent antibiotic resistance from rendering our most important medical assets obsolete.¹²⁷

While the APA petition process does hold real promise as a method to combat antibiotic resistance, there are drawbacks to this strategy. Standing is one major concern. A party seeking to challenge a decision by the FDA rejecting the petition must have standing under Article III of the Constitution in order for the decision to receive judicial review.¹²⁸ This requirement can present a major hurdle for the challenging party to overcome because of the difficulty of demonstrating injury-in-fact.¹²⁹ One way of overcoming this hurdle is to include plaintiffs who can argue a particularized harm, such as those with deficient immune systems or those who live in close proximity to animal feed lots because these individuals are particularly susceptible to the consequences of antibiotic misuse.¹³⁰

Another potential problem is the tendency of courts to show considerable deference to agencies when their actions are judicially reviewed.¹³¹ Significantly, despite numerous petitions arguing for the withdrawal of approval for drugs with major public health implications, the FDA has never withdrawn approval of a drug as a direct result of the APA petition process.¹³² However, in light of the FDA's recent shift to a tougher stance regarding antibiotic resistance, a petition may be more likely to succeed.¹³³ At the very least, a petition may offer concerned parties the opportunity to influence the

¹²⁷ *Id.* at 488–89 (“Because of the plethora of available data on the impact of animal antibiotics to human health . . . judicial review is a particularly useful tool in the case of antibiotic bans.”).

¹²⁸ See U.S. CONST. art. III, § 2, cl. 1; 5 U.S.C. § 704 (2006).

¹²⁹ See Lessing, *supra* note 116, at 484–85.

¹³⁰ *Id.* at 485–86.

¹³¹ *Id.* at 489.

¹³² *Id.* at 487; see also Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152, FDA Docket No. 2005P-0139/CP 1 (Apr. 7, 2005), available at http://www.keepantibioticsworking.com/new/resources_library.cfm?refID=70402.

¹³³ Andrews, *supra* note 117.

FDA as it revisits its policy regarding antibiotics in livestock feed in the twenty-first century.¹³⁴

In short, the APA petition process is not the perfect solution to FDA inaction regarding antibiotics in animal feed, but at the very least it could provide a means by which interested parties could exert some influence on future regulatory reform.

2. *Risk Evaluation and Mitigation Strategy*

While it is clear that physician prescription writing habits play an important role in antibiotic resistance,¹³⁵ the FDA's long standing policy of regulating only the availability of drugs as opposed to the methods in which drugs are used has prevented it from influencing physician prescription writing behavior.¹³⁶ By imposing REMS use restrictions on antibiotics that are in need of preservation, the FDA could effectively limit the misuse of antibiotics by physicians and maintain the effectiveness of these medications well into the future.

REMS restrictions permit the FDA to restrict the use of a drug in order to ensure that the benefits of its use outweigh its risks.¹³⁷ The FDA can impose a REMS restriction when a drug is initially approved, or after a drug has been approved and is currently in use, if new evidence of the risks associated with the drug comes to light.¹³⁸ If a drug sponsor does not comply with the terms of the REMS restriction, that sponsor's sale of the drug becomes unlawful.¹³⁹ The FDA may also use a REMS restriction to block the approval of new drugs, or to withdraw the approval of existing drugs.¹⁴⁰ There are six ways by which a REMS restriction can mitigate

¹³⁴ *Id.*

¹³⁵ See *supra* text accompanying notes 35–45.

¹³⁶ Evans, *supra* note 119, at 517 (“FDA long has described its role as determining which medical products are available, but letting physicians decide how the products should be used.”). See also *supra* text accompanying notes 35–45.

¹³⁷ Evans, *supra* note 119 at 511; 21 U.S.C. § 355-1(a)(2)(A) (Supp. I 2007) (allowing use restrictions on a drug that has already been approved if there is a question as to whether the benefits of using the drug outweigh its risks).

¹³⁸ Evans, *supra* note 119, at 512; see also § 355-1(a).

¹³⁹ Evans, *supra* note 119, at 512.

¹⁴⁰ *Id.* See also 21 U.S.C. § 355-1(a) (Supp. I 2007).

the risk associated with a particular drug.¹⁴¹ First, the FDA can allow a restricted drug to be prescribed only by certain practitioners, such as those with special skills or training.¹⁴² Second, the FDA can require special certification for entities that dispense a restricted drug.¹⁴³ Third, the FDA can require that drugs be administered only in specific healthcare settings.¹⁴⁴ For example, a REMS may require that a drug with sudden, life threatening side effects only be administered in a hospital setting.¹⁴⁵ Fourth, the FDA can require that patients comply with certain use conditions, such as testing prior to the administration of a drug.¹⁴⁶ Fifth, the FDA can require specific monitoring of patients to quickly detect adverse outcomes.¹⁴⁷ Finally, the FDA can require patients taking a restricted drug to enroll in a registry so their outcomes can be followed.¹⁴⁸

One way the FDA could combat antibiotic resistance would be to impose a REMS restriction on an antibiotic that is in need of preservation. By doing so, the FDA could require that physicians prescribing these medications meet the requirements of safe use as defined under the statute.¹⁴⁹ For example, the FDA could require that patients who are prescribed a REMS restricted antibiotic undergo testing to confirm the diagnosis of a bacterial infection.¹⁵⁰ This testing could ensure that the antibiotic would only be used on patients with bacterial infections instead of on patients who exaggerate symptoms or demand antibiotics for viral infections.¹⁵¹ By ensuring that an antibiotic is only used when necessary, the FDA would be able to limit the development of antibiotic resistance and prolong the life-

¹⁴¹ 21 U.S.C. § 355-1(f)(3) (Supp I 2007).

¹⁴² *Id.* § 355-1(f)(3)(A).

¹⁴³ *Id.* § 355-1(f)(3)(B).

¹⁴⁴ *Id.* § 355-1(f)(3)(C).

¹⁴⁵ *Id.*

¹⁴⁶ *Id.* § 355-1(f)(3)(D).

¹⁴⁷ *Id.* § 355-1(f)(3)(E).

¹⁴⁸ *Id.* at § 355-1(f)(3)(F).

¹⁴⁹ *Id.* at § 355-1(f).

¹⁵⁰ *Id.* at § 355-1(f)(3)(D).

¹⁵¹ See *supra* text accompanying notes 35–45.

span of a restricted treatment.

Application of a REMS restriction is not without its drawbacks. For one, it's unclear whether or not the risk of contributing to the phenomenon of antibiotic resistance through potential misuse of antibiotics outweighs the benefits of properly prescribing them.¹⁵² A REMS restriction on the use of antibiotics runs the risk of chilling the appropriate use of antibiotics and adversely affecting patient outcomes.¹⁵³ REMS restrictions on antibiotic use could also represent a serious threat to physician autonomy and impermissibly intrude into the practice of medicine.¹⁵⁴ Furthermore, improper antibiotic use in humans is only one part of a large and complex global problem.

Despite these concerns, REMS restrictions may be the most effective way for the FDA to combat antibiotic resistance in the clinical context. REMS restrictions could ensure that antibiotics are only used when appropriate and could prevent physicians from unnecessarily compounding the problem of antibiotic resistance. This outcome may justify any possible concerns regarding physician autonomy.

IV. CONCLUSION

The chronic misuse and overuse of antibiotics by humans directly contributes to the perpetuation and spread of antibiotic resistance, a growing public health problem with no viable solution in sight.

In order to effectively combat antibiotic resistance, a multifaceted approach is most likely to have the greatest impact. The first step to combating antibiotic resistance is to eliminate the addition of sub-therapeutic doses of antibiotic to livestock feed. There are several ways that this can be accomplished. Congress could use legislation to

¹⁵² 21 U.S.C. § 355-1(a)(2)(A) (Supp. I 2007); *see also* Evans, *supra* note 119, at 514 (noting that the "initial list of REMS generally included drugs with abuse or addiction potential or...severe risks.").

¹⁵³ Evans, *supra* note 119, at 518 (noting the risks associated with REMS "at both extremes: when patients are injured through physicians' undercompliance with REMS, and when physicians 'overcomply' in ways that deny their patients needed treatments.").

¹⁵⁴ *Id.*

ban the practice, but in order to do so, it must defy the powerful agribusiness lobby and risk political isolation. Punitive damages could be used as a deterrent against the use of antibiotics in livestock feed, but the chances that a lawsuit could survive the many common law hurdles it faces are slim at best. The best hope for halting the use of antibiotics in livestock feed is with regulation. The APA petition process offers a medium by which the scientific community could force the FDA to take action in combating antibiotic resistance.

The inappropriate use of antibiotics by physicians must also be addressed in order to effectively combat antibiotic resistance. The FDA's newly acquired REMS restriction authority offers the best strategy for preventing physicians from prescribing antibiotics when they are not necessary.

Finally, we must replace those antibiotics that we have driven to the brink of extinction. By leveraging intellectual property law to provide incentives for pharmaceutical companies to develop novel antibiotics, the federal government could begin to replenish a woefully inadequate antibiotic arsenal.

Without effective antibiotics, our modern civilization is no better protected against a global epidemic than our ancestors were at the time of the Black Death. We must take action in order to maintain our dominion over microbes.