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COMBATING RESISTANCE: FEDERAL EFFORTS TO REDUCE OVERUSE, CURB MISUSE, AND INCENTIVIZE THE DEVELOPMENT OF ANTIBIOTIC DRUGS

Donna Hanrahan*

INTRODUCTION

Antibiotic resistance has become a significant public health concern that stands to threaten our safety, endanger the economy, and fundamentally change the practice of modern medicine.[1] According to the Centers for Disease Control and Prevention (CDC), approximately two million people in the United States experience an antibiotic-resistant infection each year, and approximately 23,000 of them die as a result.[2] The Infectious Diseases Society of America (IDSA) has determined that methicillin-resistant Staphylococcus aureus (MRSA) alone leads to more deaths in America every year than emphysema, Parkinson˘s disease, HIV/AIDS, and homicide combined.[3] The total cost of antibiotic resistance has been estimated to be `twenty billion dollars in health care costs and thirty-five billion dollars annually in lost productivity._[4] The severity and complexity of antibiotic resistance compels national coordination. Understanding the grave threat of

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1. See generally INFECTIOUS DISEASES SOC˘Y OF AM., BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES A PUBLIC HEALTH CRISIS BREWS (2004), https://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Statements/As%20Antibiotic%20Discovery%20Stagnates%20A%20Public%20Health%20Crisis%20Brews.pdf [hereinafter BAD BUGS] (explaining the multi-faceted approach that is necessary to limit the impact of antibiotic resistance on the public).

2. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 6 (2013), http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [hereinafter ANTIBIOTIC RESISTANCE THREATS].

3. SPELLBERG ET AL., INFECTIOUS DISEASES SOC˘Y OF AM., COMBATING ANTIMICROBIAL RESISTANCE: POLICY RECOMMENDATIONS TO SAVE LIVES 1 (2011), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3738230/pdf/cir153.pdf (relying on a study conducted in 2005).

4. C. Lee Ventola, The Antibiotic Resistance Crisis: Part 1: Causes and Threats, 40 PHARMACY & THERAPEUTICS 277, 283 (2015).

antibiotic resistance, President Obama announced a series of federal actions to help fight the rise of antibiotic-resistant bacteria in September 2014.[5] However, these executive actions, absent binding legislation from Congress, fail to comprehensively address antibiotic resistance.

This article addresses the public health issue of antibiotic resistance and recommends statutory responses to reduce the overuse, curb misuse, and incentivize the development of novel antibiotic drugs. It then suggests that the Food and Drug Administration (FDA) impose a Risk Evaluation and Mitigation Strategy (REMS) restriction on novel antibiotic drug products to conserve their use and prevent misuse. Further, this article urges Congress to be swift and bold in implementing statutory reform to halt antibiotic resistance by passing the Promise for Antibiotics and Therapeutics for Health (PATH) Act to incentivize innovation in antibiotic development by creating a new regulatory approval pathway for antibiotic drugs. Until a new regulatory regime surrounding antibiotics is established, policymakers should work creatively within existing statutory frameworks to curb resistance by using the Orphan Drug Act (ODA) to spur antibiotic innovation and the Controlled Substance Act (CSA) to promote antibiotic conservation.

Part I of this article describes the public health threat of antibiotic resistance, explores the five main factors contributing to antibiotic resistance, and concludes that an effective response to antibiotic resistance must weigh each of these causes and develop effective responses in kind. Part II analyzes the role of the federal government in public health efforts, describes the recent efforts under the Obama Administration to combat antibiotic resistance, and analyzes recent FDA efforts to curb antibiotic resistance. It concludes by suggesting that the FDA impose a REMS restriction on novel antibiotic drug products to conserve their use and prevent misuse. Part III takes a historical look at the proposed legislation relating to antibiotic resistance and urges Congress to act expediently to address both conservation and innovation in the field of antibiotics by passing the PATH Act. Part IV proposes working creatively within the existing statutory framework to address both pharmaceutical innovation and antibiotic conservation in the field of antibiotics through the ODA and CSA. Finally, this article concludes by emphasizing the need for legally binding standards to reduce misuse and incentivize the development of antibiotic drugs to curb this growing public health concern.

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5. See Lisa Monaco & John P. Holdren, New Executive Actions to Combat Antibiotic Resistance and Protect Public Health, THE WHITE HOUSE: BLOG (Sept. 18, 2014, 2:33 PM), https://www.whitehouse.gov/blog/2014/09/18/new-executive-actions-combat-antibiotic-resistance-and-protect-public-health (discussing the federal actions including an Executive Order, a national strategy for combating antibiotic-resistant bacteria, a new PCAST report, and the launch of a twenty million dollar prize).

I. ANTIBIOTIC RESISTANCE

Antibiotics are drugs used to treat infections caused by bacteria.[6] With the increased use of antibiotics in the practice of medicine came a sharp decline in morbidity and mortality once associated with acute bacterial infections.[7] Antibiotics allow us to quickly and accurately treat bacterial infections, infectious diseases, foodborne illnesses, bacterial pneumonias, and other conditions in a way that would seem miraculous a century ago to those who practiced medicine.[8] Antibiotic use also expanded the practice of medicine to allow for a broader range of treatments.[9] For instance, without antibiotics, patients undergoing chemotherapy for cancer, or dialysis for renal failure, would be highly susceptible to infectious complications, which may render their treatments fatal.[10] It is difficult to imagine modern surgical procedures, such as organ transplants, without using antibiotics to prevent potentially fatal surgery-related infections.[11]

Despite their medical successes,[12] antibiotics are losing their effectiveness at an alarming rate.[13] Since bacteria are highly adaptive microorganisms,[14] no matter how carefully they are used, antibiotics intrinsically create evolutionary pressure for resistance.[15] This phenomenon has been

6. See Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture: Hearing Before the Subcomm. on Health of the Comm. on Energy & Commerce, 111th Cong. 33 (2010) (statement of Joshua M. Sharfstein, Principal Deputy Comm˜r, Food & Drug Admin.).

7. See CTRS. FOR DISEASE CONTROL & PREVENTION, Achievements in Public Health, 1900-1999: Control of Infectious Diseases, 48 MORBIDITY & MORTALITY WKLY. REP. 621, 621˜22 (1999) (showing that after the first use of penicillin, the introduction of the Salk Vaccine, and the Passage of the Vaccination Assistance Act, mortality was at its lowest in the late 20th century).

8. See WHITE HOUSE, NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA 1 (2014), https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf [hereinafter NATIONAL STRATEGY].

9. See Cesar A. Arias & Barbara E. Murray, Antibiotic-Resistant Bugs in the 21st Century´ A Clinical Super-Challenge, 360 NEW ENG. J. MED. 439, 439-40 (2009) (pointing to the critical role of antibiotics in the treatments for cancer, HIV, and MRSA and the developments in surgery and transplantations).

10. ANTIBIOTIC RESISTANCE THREATS, supra note 2, at 5.

11. Arias & Murray, supra note 9, at 439.

12. See Fernando Bacquero & Jesßs Bl®quez, Evolution of Antibiotic Resistance, 12 TRENDS ECOLOGY & EVOLUTION 482, 482 (1997) (noting that antibiotics represent the `protective umbrella_ under which advancements in modern medicine, such as intensive care, advanced surgery, chemotherapy, and organ transplantation, have been developed).

13. BAD BUGS, supra note 1, at 9.

14. See Vanessa K.S. Brice¿o, Superbug Me: The FDA˜s Role in the Fight Against Antibiotic Resistance, 9 N.Y.U. J. LEGIS. & PUB. POL˜Y 521, 522 (2005).

15. See D. J. Austin et al., The Relationship Between the Volume of Antimicrobial Consumption in Human Communities and the Frequency of Resistance, 96 PROC. NAT˜L ACAD. SCI. 1152, 1152 (1999).

exacerbated by society˘s chronic misuse and overuse of antibiotics.[16] Antibiotic resistance results when bacteria mutate, or acquire new genes, in ways that reduce or eliminate the effectiveness of antibiotics.[17] The majority of microorganisms, which have little resistance to the antibiotic, are destroyed, while those with the highest resistance reproduce their genetic information.[18] This process may occur until an entire bacterial species becomes resistant to a certain antibiotic.[19]

Alexander Fleming, the father of antibiotics who developed penicillin in 1928, had the foresight to warn against the misuse of antibiotics and predicted the dangerous phenomenon of resistance.[20] In his 1945 Noble Prize acceptance speech, he cautioned that, `the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug that make them resistant._[21] Then, in 1967, U.S. Surgeon General William H. Stewart asserted, `[t]he time has come to close the book on infectious diseases._[22] Nearly half a century later, that book is still open precariously wide. Moreover, the economic cost of antibiotic resistance is steep.[23] Indeed, each day, policymakers fail to act, and it becomes more difficult and increasingly expensive to address drug resistance in the future.[24]

A. Factors Contributing to Antibiotic Resistance

Antibiotic-resistant organisms arise from many factors cumulatively and cannot be reduced to a single cause.[25] Factors contributing to antibiotic

16. See STUART B. LEVY, THE ANTIBIOTIC PARADOX: HOW THE MISUSE OF ANTIBIOTICS DESTROYS THEIR CURATIVE POWERS (2d ed. 2002); see also Ventola, supra note 4, at 277¯283 (illustrating how a physicians˘ tendency to over-prescribe and patients˘ tendency to fail in completing the course of treatment are two societal factors which have contributed to antibiotic resistance).

17. NATIONAL STRATEGY, supra note 8, at 4.

18. DAN J. TENNENHOUSE, 2 ATTORNEY˘S MEDICAL DESKBOOK í 22:24, Westlaw (database updated Oct. 2015).

19. See Bacquero & Bl®quez, supra note 12, at 484.

20. Alexander Fleming, Penicillin, Nobel Lecture (Dec. 11, 1945) in NOBEL LECTURES 83, 93, http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf.

21. Id.

22. See, e.g., Ross Upshur, Ethics and Infectious Disease, 86 BULL. WORLD HEALTH ORG. 654, 654 (2008), http://www.who.int/bulletin/volumes/86/8/08-056242/en/.

23. See BAD BUGS, supra note 1, at 10.

24. Press Release, Ctrs. for Disease Control & Prevention, CDC Year in Review: `Mission: Critical_ (Dec. 15, 2014), http://www.cdc.gov/media/releases/2014/p1215-2014-year-in-review.html.

25. INST. OF MED. FORUM ON EMERGING INFECTIONS, 5 Factors Contributing to the Emergence of Resistance, in THE RESISTANCE PHENOMENON IN MICROBES AND INFECTIOUS DISEASE VECTORS: IMPLICATIONS FOR HUMAN HEALTH AND STRATEGIES FOR CONTAINMENT: WORKSHOP SUMMARY 130, 130 (Stacey L. Knobler et al. eds., The National Academies Press 2003), https://www.ncbi.nlm.nih.gov/books/NBK97126.

resistance include: (1) overuse through over-prescription, (2) misuse through failure to complete course of treatment, (3) failure to contain antibiotic-resistant infections in healthcare settings, (4) factory farming and subtherapeutic use in meat products, and (5) barriers to pharmaceutical innovation given the current patent system and the price/volume business model on which the industry currently operates.[26] Each factor must be considered to develop an effective response to antibiotic resistance.

1. Overuse Through Over-Prescription

Antibiotic resistance is perpetuated by the excessive use of antibiotics in humans.[27] The CDC estimates that approximately fifty percent of all the antibiotics prescribed for patients in the United States are unnecessary or not optimally prescribed.[28] In addition, many physicians erroneously recommend antibiotics for viral infections.[29] This is due in part to the appearance of a tangible medical intervention, as compared to the indirect relief of symptoms or a mere `wait it out_ approach.[30] Many patients insist on receiving novel antibiotics when other approaches may be equally, or in some cases more, efficient.[31] This phenomenon demonstrates that physicians may be `acquiescing to their patients˘ demands in order to deliver a positive treatment outcome and retain the patients˘ business._[32] Physicians must keep these concerns about overuse in mind and prescribe antibiotics prudently to preserve the limited amount of effective medications.[33]

Antibiotic cycling is one antibiotic utilization strategy that may slow the development of antibiotic resistance. Antibiotic cycling occurs when different classes of antibiotics are deliberately alternated and rotated in a given population for a period of time.[34] As early as the 1980s, the Minneapolis Veterans˘ Affairs Medical Center˘s cycling efforts of the antibiotics gentamicin, tobramycin, and amikacin effectively reduced gentamicin resistance.[35] However, cycling policies are difficult to enforce

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26. See Ventola, supra note 4, at 277¯283.
27. See ANTIBIOTIC RESISTANCE THREATS, supra note 2, at 11.
28. Id.
29. See Cory Fox, Resisting Antibiotic Resistance: Legal Strategies to Maintain Man˘s Dominion Over Microbes, 12 HOUS. J. HEALTH L. & POL˘Y 35, 42 (2011).
30. Richard S. Saver, In Tepid Defense of Population Health: Physicians and Antibiotic Resistance, 34 AM. J. L. & MED. 431, 471 (2008).
31. Fox, supra note 29, at 41¯42.
32. Id. at 42.
33. See Saver, supra note 30, at 435.
34. See Erwin M. Brown & Dilip Nathwani, Antibiotic Cycling or Rotation: A Systematic Review of the Evidence of Efficacy, 55 J. ANTIMICROBIAL CHEMOTHERERAPY 6, 6 (2005).
35. Joseph F. John, Jr., Editorial, Antibiotic Cycling: Is It Ready For Prime Time?, 21.1 INFECTION CONTROL & HOSP. EPIDEMIOLOGY 9, 9¯10 (2000) (explaining that gentamicin,

and efforts have been sporadic at best.[36] Many factors can affect the outcome of cycling programs, such as which antibiotics are cycled, the order in which they are cycled, and the length of each cycle.[37] Healthcare institutions must carefully adjust these factors and optimize antibiotic utilization strategies for their particularized setting to succeed in reducing resistance.

2. Misuse Through Failure to Complete Course of Treatment

Many patients unknowingly contribute to antibiotic resistance by failing to complete their entire course of treatment, thus failing to eradicate the infection from their bodies.[38] Patients often stop taking their antibiotics when their symptoms improve because they do not recognize that the drug has not yet effectively eliminated the underlying bacteria.[39] This causes eradication of bacteria with the weakest resistance, but high-resistance bacteria will remain and reproduce.[40] Many patients remain unaware that such behavior can help fuel antibiotic resistance problems.[41]

To prevent misuse and curb antibiotic resistance, patients must take greater responsibility toward their treatments. Moreover, physicians must find innovative ways to sufficiently educate their patients and support adherence.[42] Physicians must take time to emphasize the need to adhere to dosage amounts and length of treatment in order to maximize the benefit to the patient and minimize resistance problems.[43] Methods to increase medication adherence must also be developed. These adherence methods could range from high tech mobile applications and `smart_ pill bottles to simple and cheap methods, such as adding a milestone to a treatment (i.e. advising patients to complete ten white pills before completing five blue pills of the same drug) to increase adherence.[44] These measures will help patients

tobramycin, and amikacin fall under the antibiotic category of aminoglycosides, used in the treatment of gram-negative bacterial infections); Marie-Paule Mingeot-Leclercq et al., Aminoglycosides: Activity and Resistance, 43 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 727, 727 (1999).

36. See Erwin M. Brown & Dilip Nathwani, Antibiotic Cycling or Rotation: A Systematic Review of the Evidence of Efficacy, 55 J. ANTIMICROBIAL CHEMOTHERERAPY 6, 6-9 (2005) (discussing the methodological flaws and lack of standardization that render the results of studies evaluating the efficacy of antibiotic cycling to be unreliable, as many issues relating to cycling remain unaddressed).

37. Id. at 8¯9.

38. See Fox, supra note 29, at 41.

39. Bacquero & Bl®quez, supra note 12, at 485.

40. TENNENHOUSE, supra note 18.

41. Id.

42. See Saver, supra note 30, at 472.

43. See id. at 450 (explaining that physician management of antibiotics must extend to beyond prescribing and include monitoring and counseling use).

44. E. Patchen Dellinger et al., Quality Standard for Antimicrobial Prophylaxis in

complete their treatment and maximize the effect of antibiotics.

3. Failure to Contain Antibiotic-Resistant Infections in Healthcare Settings

Hospital-acquired infections that spread resistant bacterial strains among inpatients and healthcare facility staff far exceed what we should be willing to tolerate.[45] Institution-acquired antibiotic infections can be caused by breaches in safety and infection control protocol in healthcare settings, including hospitals and nursing homes.[46] Patients with antibiotic-resistant infections and non-infected susceptible patients are often kept in close proximity, even though physical separation of patients is preferred.[47] Deviations from protocol, such as hand washing or sterilization of equipment, can also have devastating effects.[48] For example, in February 2015, the UCLA Health System linked the deaths of two patients to a superbug known as carbapenem-resistant enterobacteriaceae (CRE) as a result from unsterilized endoscopy equipment.[49] CRE is resistant to virtually all known antibiotics and kills up to fifty percent of people infected.[50] Some patients who acquired these deadly CRE bacteria were fairly healthy and receiving routine endoscopies.[51] This is a sad example of the health system failures that result in patients leaving sicker than they had arrived, or worse yet, not leaving at all.

Seventy percent of hospital-acquired infections are resistant to at least one antibiotic.[52] Moreover, the FDA has estimated that approximately 150,000 hospital-acquired infections involve resistant strains of bacteria annually, resulting in an extra $375 million in hospital charges per year.[53] The

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Surgical Procedures, 18 CLINICAL INFECTIOUS DISEASES 422, 422 (1994) (emphasizing the need to determine optimal timing, dose and duration for drug therapy).

45. See Saver, supra note 30, at 432 (explaining that drug-resistant hospital-acquired infections cause more deaths per year than `HIV-AIDS, Parkinson¨s, emphysema, or homicide_).

46. See generally AMY S. COLLINS, Chapter 41 Preventing Health Care-Associated Infections in PATIENT SAFETY AND QUALITY: AN EVIDENCE-BASED HANDBOOK FOR NURSES (2008), https://www.ncbi.nlm.nih.gov/books/NBK2683/ (discussing systematic antibiotic controls in health care settings and how they impact the rate of hospital acquired infections).

47. See generally Ruth M. Kleinpell et al., Chapter 42 Targeting Health Care-Associated Infections: Evidence-Based Strategies in PATIENT SAFETY AND QUALITY: AN EVIDENCE-BASED HANDBOOK FOR NURSES: VOL. 2 2-577 (2008), https://www.ncbi.nlm.nih.gov/books/NBK2632/pdf/Bookshelf_NBK2632.pdf.

48. Id. at 2-577¯78.

49. Bill Briggs, UCLA :Superbug¨ Patient to Sue Maker of Suspect Endocopes, NBC NEWS (Feb. 20, 2015), http://www.nbcnews.com/health/health-news/ucla-superbug-patient-sue-maker-suspect-endocopes-lawyer-n309891.

50. Id.

51. Id.

52. BAD BUGS supra note 1, at 3.

53. Saver, supra note 30, at 441.

pervasiveness of antibiotic-resistant infections can transform hospitals into health threats due to the increased presence of MRSA and other common, yet dangerous, infections.[54]

Rather than blame, there needs to be greater accountability for healthcare safety practices at the systemic level. The medical community should address how to better improve adherence to simple, yet effective approaches to safety, including hand-washing, checklists, and personal protective equipment monitoring to avoid the pitfalls that place healthcare workers at risk when treating patients with infectious diseases. Then, we will be able to comfortably rely on established health and safety protections.

4. Factory Farming & Meat Products

Antibiotics have been administered in livestock for nontherapeutic purposes, namely to promote the growth of livestock for human consumption, without any investigation into potential consequences.[55] Starting in the late 1940s, livestock have been subjected to sub-therapeutic levels of antibiotics simply so that they can grow larger, known as the `antibiotic growth effect._[56] With the increase in `factory farms_ in the early 2000s, this issue was exacerbated, as it is nearly impossible to prevent the spread of disease among animals kept in such close quarters.[57] Food-related Salmonella and E. coli outbreaks suggest that these diseases may be passed to humans when the animals are slaughtered and eaten.[58] In addition, resistant bacteria can spread from food animals to humans through manure and other environmental factors.[59] For these reasons, subtherapeutic use of antibiotics in livestock is a primary factor contributing to antibiotic resistance.[60]

5. Pharmaceutical Innovation & Patent Law

The research and development (R&D) of new antibiotics has sharply

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54. See Lauren Orrico, Squashing the Superbugs: A Proposed Multifaceted Approach to Combatting Antibiotic-Resistant Bacteria, 27 J. OF L. & HEALTH 259, 269 (2014).

55. See Jay P. Graham et al., Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis, 122 PUB. HEALTH REPS. 79, 80 (2007) (explaining the health concerns and lack of testing for animal antibiotics).

56. Id.

57. See Factory Farm Nation: How America Turned its Livestock Farms into Factories, FOOD & WATER WATCH 2 (Nov. 2010), http://www.factoryfarmmap.org/wp-content/uploads/2010/11/FactoryFarmNation-web.pdf (`Crowded, unsanitary conditions leave animals susceptible to disease, drive the overuse of antibiotics and hormone treatments, and can contribute to foodborne illnesses._) [hereinafter Factory Farm Nation].

58. See Karen Florini & Rebecca J. Goldburg, Playing Chicken With Antibiotics, 22 ENVTL. F. 22, 23¯24 (2005) (discussing the rapid spread of disease and the resistance of antibiotics).

59. Factory Farm Nation, supra note 57, at 2.

60. Id.

declined in recent decades.[61] Thus, we are left without a pipeline of novel antibiotics to replace those gradually lost to antibiotic resistance.[62] Large pharmaceutical companies, once trailblazers in the field of antibiotic R&D, have since shifted their focus to more profitable research activities.[63] For instance, United States antibiotic sales peaked in 2005 and have subsequently declined compared to other prescription drugs.[64] Relatedly, the total number of new antibacterial agents approved by the FDA has declined consistently over the last twenty-five years.[65] For example, the FDA approved sixteen new systemic antibacterial agents in 1983-1987,[66] yet approved only two new systemic antibacterial agents from 2008-2012.[67]

R&D is often associated with time-consuming and expensive regulatory challenges associated with conducting the clinical trials needed for new drug approval, and research in antibiotic drug development is no exception.[68] One of the most significant reasons for the failure in antibiotic drug development is the low economic return that makes the development of novel antibiotics an unattractive investment.[69] Since the pharmaceutical industry operates on a price/volume model, it demands that R&D funds be allocated where return on investment (ROI) is greatest, thus incentivizing investment in products that will sell at the greatest volume or at the highest price.[70]

Unfortunately, the ROI for antibiotics is low.[71] First, lost-cost generic

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61. The decline in R&D investment began over ten years ago. In 1990, half of the large pharmaceutical companies in the United States and Japan either halted or decreased their antibiotic discovery efforts. This trend continued in 2000 when spun off its anti-infective discovery division. Furthermore, Bristol-Myers Squibb Company Abbott Laboratories, Eli Lilly and Company, and Wyeth all halted or substantially reduced their anti-infective discovery efforts in 2002. More companies continue to indicate a decline in their R&D efforts. BAD BUGS, supra note 1, at 14.

62. 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 OXFORD J. CLINICAL INFECTIOUS DISEASES 155, 155 (2008), www.idsociety.org/workarea/downloadasset.aspx?id=9048.

63. See BAD BUGS, supra note 1, at 3.

64. Kevin Outterson et al., Repairing the Broken Market for Antibiotic Innovation, 34 HEALTH AFF. 277, 278¯79 (2015), http://content.healthaffairs.org/content/34/2/277.abstract.

65. Spellberg et al., supra note 62, at 158.

66. BAD BUGS, supra note 1, at 15.

67. Mari Sevebrov, U.S. Goes On The Offensive To Keep Superbugs In Check, BIOWORLD, http://www.bioworld.com/content/us-goes-offensive-keep-superbugs-check-0 (last visited Nov. 14, 2016).

68. See Cindy R. Friedman & Cynthia G. Whitney, It˘s Time for a Change in Practice: Reducing Antibiotic Use can Alter Antibiotic Resistance, 197 J. INFECTIOUS DISEASES 1082, 1082 (2008).

69. Outterson et al., supra note 64, at 279.

70. See id. at 278.

71. Id. at 279.

antibiotics are available in the majority of clinical circumstances.[72] In fact, the antibiotics drugs are so inexpensive that despite accounting for 6.4 percent of all U.S. prescriptions in 2013 by volume, they composed only 2.6 percent of prescriptions by value.[73] Second, market uptake is limited, due in part to public health efforts to curb unnecessary antibiotic prescriptions.[74] In order to prevent antibiotic resistance, the use of novel antibiotics are systemically discouraged, except for in the most extreme cases.[75] Thus, profitability is limited.[76] Ironically, antibiotics are sometimes seen as `victims of their own success._[77] While they are often more effective than their alternatives, their use must be limited to maintain their efficacy and yield an individual and public health benefit.[78] With the rise of antibiotic education and stewardship programs, the market for new antibiotics will continue to be appropriately restricted.[79] Third, the lower rate of ROI on antibiotics, as compared to other products, is due in part to their short-term therapeutic use. Not only are antibiotic treatments temporary by nature, they completely cure the target disease as well.[80]

Fourth, the value of antibiotics cannot be appropriately quantified, as the value of the drugs˘ benefit extends beyond patient use´ the broader population also stands to benefit from the targeted use of new antibiotics by not developing costly, and possibly deadly, antibiotic-resistant infections.[81] This public health value is not captured in willingness to pay and thus it is not reflected in pricing models.[82] Aaron S. Kesselheim, an instructor in medicine in the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, at Brigham and Women˘s Hospital and Harvard Medical School, and Kevin Outterson, an associate professor of law at the Boston University School of Law, both experts in antibiotic resistance, contend that the `current legal structures and market incentives unwittingly accelerate resistance in several ways, all rooted in the mismatch between private and social value._[83] They argue that the substantial

72. Id. at 278.
73. Id.
74. Id.
75. See E. Power, Impact of Antibiotic Restrictions: The Pharmaceutical Perspective, 12 CLINICAL MICROBIOLOGY & INFECTION 25, 29 (2006).
76. Id.
77. Spellberg et al., supra note 62, at 158.
78. Id.
79. Outterson et al., supra note 64, at 278.
80. Spellberg et al., supra note 62, at 158.
81. Outterson et al., supra note 64, at 278.
82. Id.
83. Aaron S. Kesselheim & Kevin Outterson, Improving Antibiotic Markets for Long Term Sustainability, 11 YALE J. HEALTH POL˘Y, L. & ETHICS 101, 105 (2011).

divide between the private and social value of antibiotics has led to a troubling supply and demand incentives and an increase in antibiotic-resistant infections. Further, they maintain that `the patent system helps spur innovation of new drugs, but pending patent expiration may lead antibiotic manufacturers to waste their products by promoting drug use for a broad array of minor clinical conditions, rather than trying to assure that their products are limited to the most urgent cases._[84] Thus, the development of antibiotic therapies is not profitable in a patent-centered market which requires pharmaceutical companies to capitalize on sales during the drug˘s patented years, as antibiotics are only effective if their use is conserved.

Large publicly traded pharmaceutical companies, despite having beneficent mission statements and legitimate aims of developing novel medical treatments for the public benefit, are also beholden to their shareholders.[85] The pharmaceutical industry could reasonably determine that it is not economically viable to risk expending capital on antibiotic R&D when other drug categories have higher earning potential.[86] Thus, it would be reasonable for a publicly traded company to reject antibiotics R&D in pursuit of a new `Blockbuster_ drug for a therapeutic area with a wider patient population.[87] Indeed, as of 2008, only five of the fifty largest pharmaceutical companies are home to active antibiotic-development programs.[88] Bearing this in mind, it comes as no surprise that companies are dissuaded from investing in the development of antibiotic drugs.

Even when drug companies invest in R&D for antibiotics, they are drawn only to the largest markets.[89] Of the six most dangerous groups of microorganisms demonstrating increasing rates of antibiotic resistance, only MRSA has seen some advancement due to its clinical notoriety and increased market incentives.[90] On the other hand, the remaining five priority pathogens with smaller potential markets have far fewer new agents in the pipeline.[91] Comprehensive and coordinated planning among various sectors of the healthcare industry is necessary to overcome this tension between pharmaceutical innovation and antibiotic conservation.

Antibiotic resistance arises from many factors cumulatively, and thus

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84. Id.

85. See Spellberg et al., supra note 62, at 161 (explaining that `corporate directors have a fiduciary responsibility to invest their R&D dollars in a manner that maximizes the likelihood of return on investment._).

86. Id.

87. See id.

88. Theresa Braine, Race Against Time to Develop New Antibiotics, 89 BULL. WORLD HEALTH ORG. 88, 88˘89 (2011), http://www.who.int/bulletin/volumes/89/2/11-030211/en/.

89. Kesselheim & Outterson, supra note 83, at 120.

90. Id. at 117˘18.

91. Id.

requires a multifaceted response. An effective response to antibiotic resistance must give weighted consideration to each of these causes and develop effective strategies in kind. Having explored the economic and social cost of antibiotic resistance and the factors contributing the phenomenon, Part II will now explore the role of the federal government in public health, analyze recent efforts under the Obama Administration, and propose that the FDA implement a REMS restriction as a solution to combat antibiotic resistance.

II. FEDERAL EFFORTS TO COMBAT ANTIBIOTIC RESISTANCE

Antibiotic resistance is an imminent public health concern that requires national coordination, and is therefore ripe for federal action. Understanding the severity of the public health threat, President Obama launched an executive campaign in 2014 to reduce the chronic overuse of antibiotics, as well as to incentivize the development of novel antibiotic drugs.[92] Foremost, Executive Order 13676, titled `Combating Antibiotic-Resistant Bacteria,_ calls for (1) improved monitoring of resistant infections; (2) more stringent regulations governing antibiotic use; (3) more robust research to innovate treatments; and (4) greater international cooperation to address the issue of antibiotic-resistant bacteria.[93] The Executive Order also demands that the Task Force submit a five year National Action Plan (`Action Plan_), including goals, milestones, timelines, and metrics for measuring progress.[94]

In addition, as a part of these executive efforts to combat antibiotic resistance, President Obama announced that the National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA) launched a $20 million prize to `facilitate the development of a rapid diagnostic test to be used by health care providers to identify highly resistant bacterial infections at the point of patient care._[95] President Obama also requested that the President˘s Council of Advisors on Science and Technology (PCAST) create a National Report on Combating Antibiotic Resistance.[96] Further, President Obama charged the National Security Council (NSC) and the Office of Science and Technology Policy (OSTP) to create a National Strategy for Combating Antibiotic Resistance.[97] These reports have been completed, and they establish broad goals to slow the emergence of resistant bacteria and prevent the spread of resistant

92. See generally Combating Antibiotic-Resistant Bacteria, 184 Fed. Reg. 56, 931 (Sept. 23, 2014).
93. Id.
94. Id.
95. Monaco & Holdren, supra note 5.
96. NATIONAL STRATEGY, supra note 8, at 1.
97. Combating Antibiotic-Resistant Bacteria, 184 Fed. Reg. 56, 931.

infections, strengthen surveillance, accelerate R&D for new antibiotics, and improve international collaboration.[98]

While these calls to action are certainly welcomed, these measures remain little more than `feel good_ actions without statutory and regulatory teeth. Taking President Obama¨s lead, the FDA and Congress should implement statutory reform to halt antibiotic resistance as a mounting public health concern, while simultaneously preserving incentives to continue developing new antibiotics.

A. The Role of the FDA

The FDA recognized antibiotic resistance as a health concern as far back as 1977, but has yet to effectively limit the use of antibiotics for human disease prevention and growth promotion in food animals.[99] Despite its criticisms for inaction, the FDA has taken some steps towards regulating antibiotics to prevent overuse and abuse in livestock.[100] The FDA issued two Guidances for Industry (GFI #209 and #213) that request voluntarily phasing out antibiotics in livestock for production purposes and advise that licensed veterinarians should oversee uses of antibiotic drugs in livestock.[101] These GFIs also advise that animal drug companies should change their labels on drugs to withdraw any claims that such drugs can be used for growth promotion.[102]

The FDA has also taken steps towards regulating antibiotics to prevent overuse and abuse in humans through labeling requirements.[103] As of 2003, the FDA requires that antibiotic labels display information about the risks of antibiotic resistance by reminding physicians that the drug should be used only to treat infections proven or highly suspected to be bacterial in order to

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98. NATIONAL STRATEGY, supra note 8, at 1¯2.

99. Nat. Res. Def. Council, Inc. v. U.S. FDA, 884 F. Supp. 2d 127, 134¯36 (S.D.N.Y. 2012).

100. See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY #209, THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS 9 (2012), http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ ucm216936.pdf [hereinafter GUIDANCE FOR INDUSTRY #209]; see also U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY #213, NEW ANIMAL DRUGS AND NEW ANIMAL DRUG COMBINATION PRODUCTS ADMINISTERED IN OR ON MEDICATED FEED OR DRINKING WATER OF FOOD-PRODUCING ANIMALS: RECOMMENDATIONS FOR DRUG SPONSORS FOR VOLUNTARILY ALIGNING PRODUCT USE CONDITIONS WITH GFI #209 8 (2013), http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf [hereinafter GUIDANCE FOR INDUSTRY #213].

101. GUIDANCE FOR INDUSTRY #209, supra note 100, at 9; GUIDANCE FOR INDUSTRY #213, supra note 100, at 8.

102. GUIDANCE FOR INDUSTRY #209, supra note 100, at 9; GUIDANCE FOR INDUSTRY #213, supra note 100, at 8.

103. Saver, supra note 30, at 466.

combat antibiotic resistance.[104] The drug label must also advise physicians to use appropriate screening tests to prescribe the proper antibiotic.[105] Lastly, the label must remind physicians to counsel their patients to follow their course of treatment from start to finish to avoid resistance problems.[106] However, these labeling requirements are often ignored by prescribing physicians and have had little influence on prescribing practices.[107]

B. REMS for Antibiotics

The FDA has the capacity to regulate the use of antibiotics in humans and animals through its authority to establish REMS restrictions.[108] REMS was created as a part of the Food and Drug Administration Amendments Act of 2007 (FDAAA).[109] REMS restrictions allow the FDA to limit the use of a particular drug to instances where its benefits are likely to outweigh its risks by mandating additional post-market requirements.[110] The FDA may use REMS restrictions to limit access to new or existing drugs, block the approval of new drugs, or withdraw the approval of existing drugs.[111] The FDA can impose a REMS restriction in many forms, hinging on elements to assure safe use, including: (1) allowing a restricted drug to be prescribed only by certain practitioners with special qualifications;[112] (2) requiring certification for entities that dispense a restricted drug;[113] (3) requiring that drugs be administered only in specific healthcare settings, rather than at home;[114] (4) requiring that patients comply with certain conditions of use;[115] (5) requiring patients to be monitored to detect adverse events;[116] and (6) requiring patients taking a restricted drug to enroll in a registry to surveil outcomes.[117] The FDA can impose a REMS restriction at any time in a drug˘s lifecycle.[118] REMS restrictions have also been effective in practice, as in 2012,[119] when the FDA

104. 21 C.F.R. í 201.24 (2008).
105. Saver, supra note 30, at 466.
106. Id.
107. Id. at 468.
108. 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).
109. Id.
110. 21 U.S.C. í 355-1(a)(2)(A) (2008).
111. Fox, supra note 29, at 58.
112. 21 U.S.C. í 355-1(f)(3)(A).
113. 21 U.S.C. í 355-1(f)(3)(B).
114. 21 U.S.C. í 355-1(f)(3)(C).
115. 21 U.S.C. í 355-1(f)(3)(D).
116. 21 U.S.C. í 355-1(f)(3)(E).
117. 21 U.S.C. í 355-1(f)(3)(F).
118. Evans, supra note 109, at 512.
119. See Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids, U.S. FOOD & DRUG ADMIN., www.fda.gov/Drugs/DrugSafety/Informat

used REMS to restrict the distribution of over twenty narcotics, most closely associated to drug-related deaths in the United States.[120] Further, the FDA may impose civil monetary penalties for violations of the REMS provisions, in addition to the deeming the drug misbranded.[121]

While the FDA has yet to use REMS restrictions for any antibiotic products, it is certainly within their purview to do so.[122] A novel antibiotic, whose efficacy and longevity depends on its limited use, warrants a REMS restriction to protect the public health.[123] In the context of antibiotics, REMS restrictions would aim to limit the prescription of a certain antibiotic drug to instances where they are absolutely clinically necessary.[124] For example, the FDA could require that patients undergo testing to confirm the type of bacterial infection before being prescribed a REMS-restricted antibiotic or place limits on physicians˘ prescribing abilities.[125] Imposing a REMS restriction could therefore effectively reduce the rate of antibiotic resistance and prolong the effective lifespan of the drug.[126]

Some fear that REMS restrictions to conserve antibiotics in the clinical context may threaten physician autonomy by interfering with the practice of medicine.[127] Congress intended the Federal Food, Drug, and Cosmetic Act (`FD&C Act_) to regulate the safety of drugs, but did not allow for it to inhibit a physician˘s ability to prescribe drugs, once they have been approved.[128] REMS restrictions run the risk of a having a chilling effect on antibiotic prescriptions to patients who actually need them, thereby adversely affecting patient outcomes.[129] However, in clinical practice, a REMS restriction is not likely to limit patient access. Rather, the system merely adds a system of checks on the prescribing physician to affirm that the drug is

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ionbyDrugClass/ucm163647.htm (last visited Nov. 14, 2016) (providing an example of REMS restriction usage in 2012).

120. Questions and Answers: FDA approves a Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm (last updated Mar. 1, 2013).

121. Evans, supra note 109, at 521˘22.

122. See Fox, supra note 29, at 59 (describing the ways in which the FDA could use REMS restrictions if they chose).

123. Id. (explaining that through a REMS restriction, `the FDA could require that physicians prescribing these medications meet the requirements of safe use as defined under the statute._).

124. Id. at 59.

125. Id. (explaining that antibiotics should only be used for bacterial infections and not viral infections).

126. See Fox, supra note 29, at 59˘60.

127. See id. at 60.

128. See JAMES ROBERT NIELSEN, HANDBOOK OF FEDERAL DRUG LAW 38 (George Mundorff & Susan Hunsberger eds., 2d ed. 1992).

129. Fox, supra note 29, at 60.

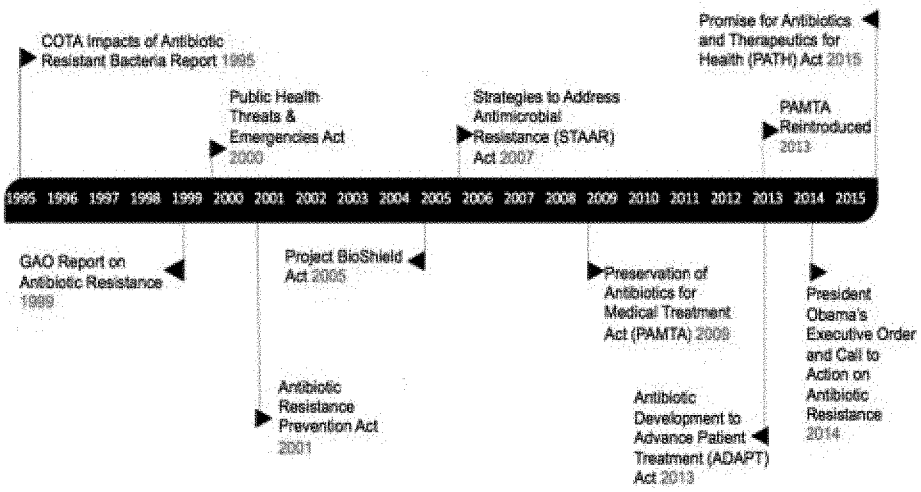
clinically necessary before prescribing it.[130] Further, critics may argue that the REMS render drug lifecycle management more costly and complex.[131] Still, this is a small burden to bear compared to the large public health threat of antibiotic resistance.

Lastly, while a REMS restriction may adequately address the issue of antibiotic conservation, it is just one piece of the puzzle.[132] The issue of antibiotic innovation remains unresolved by this solution, necessitating further action by Congress. Having described the executive branch˘s actual and potential efforts to combat antibiotic resistance, Part III turns to Congress˘ role in combating the growth of antibiotic-resistant bacterial strains.

III. CONGRESS˘ ROLE IN COMBATTING ANTIBIOTIC-RESISTANT BACTERIAL STRAINS

The growth of antibiotic-resistant bacteria may be slowed through congressional action.[133] For the past 30 years, Congress has struggled to establish legislative strategies to reduce the overuse, curb misuse, and incentivize the development of novel antibiotic drugs.[134] For example, as described in Figure 1 below, several bills have been introduced in Congress

Figure 1. Proposed Antibiotic-Related Legislation Timeline



130. See id. at 60 (explaining that REMS restrictions would curtail inappropriate antibiotic use).

131. Evans, supra note 109, at 515.

132. See Fox, supra note 29, at 60 (describing that REMS is one part of the larger global problem associated with inappropriate antibiotic use).

133. Orrico, supra note 54, at 283˘84.

134. Id. at 277.

to address antibiotic resistance with little success.[135] To adequately address this public health concern, Congress must act expediently to address both conservation and innovation in the field of antibiotics.

In 1995, Congress first addressed the issue of antibiotic resistance with the Congressional Office of Technology Assessment (COTA) and its Impacts of Antibiotic Resistant Bacteria report.[136] Then, the General Accounting Office (GAO) issued another report to Congress warning about the emergence, spread, and threat of antibiotic resistance in 1999.[137] In 2000, the Public Health Threats and Emergencies Act aimed to establish an Antimicrobial Resistance Task Force to coordinate federal programs and provide grants to combat antibiotic resistance.[138] Shortly after, in 2001, the Energy and Commerce Committee presented the Antibiotic Resistance Prevention Act, which aimed to fund antibiotic resistance awareness and research.[139] However, neither of these bills ever garnered enough support to pass into law.[140]

In 2005, Senator Joseph Lieberman (D-CT) introduced the Project BioShield II Act.[141] The bill aimed to boost R&D to countermeasure against biological, chemical, nuclear, and radiological weapons, in addition to infectious disease outbreaks.[142] The bill included a `wild-card patent term extension_ in which `the patent holder for a novel antibiotic or counterterrorism agent would receive a patent term extension_ of three months to two years that may `be applied either to the antibiotic, the counterterrorism agent, or any other patent held by the patent owner._[143] The bill was never acted upon after its initial hearing following pushback from lobbying groups representing generic pharmaceutical

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135. Andrew Geltman, Defusing the Bug Bomb: Legal Strategies to Combat Antibiotic Resistant Infections, 18 J. HEALTH CARE L. & POL'Y 115, 117 (2015).

136. See generally U.S. CONG., OFF. OF TECH. ASSESSMENT, OTA-H-6298, IMPACTS OF ANTIBIOTIC-RESISTANT BACTERIA iii (1995), http://ota.fas.org/reports/9503.pdf (discussing what was known about antibiotic-resistant bacteria and describing research and development directed at controlling them).

137. See generally U.S. GOV'T ACCOUNTABILITY OFF., GAO-99-132, ANTIMICROBIAL RESISTANCE: DATA TO ASSESS PUBLIC HEALTH THREAT FROM RESISTANT BACTERIA ARE LIMITED (1999), http://www.gao.gov/assets/230/227221.pdf (discussing what was known about the public health burden due to antimicrobial resistance and forecasting the potential future burden).

138. Public Health Threats and Emergencies Act, H.R. 4964, 106th Cong. (2000); Fox, supra note 29, at 49.

139. Antibiotic Resistance Prevention Act of 2001, H.R. 1771, 107th Cong. (2001); Fox, supra note 29, at 49.

140. Fox, supra note 29, at 49.

141. Project Bioshield II Act of 2005, S. 975, 109th Cong. í 301 (2005).

142. Id.; Jessica P. Schulman, Patents and Public Health: The Problems with Using Patent Law Proposals to Combat Antibiotic Resistance, 59 DEPAUL L. REV. 221, 231 (2009).

143. Schulman, supra note 142, at 231¯32.

manufacturers.[144] Many expressed concerns that these measures would inevitably delay access to affordable medicine. A similar bill, sans wild-card extension, was introduced in 2006 but remained unsuccessful.[145]

In September 2007, Representatives Matheson (D-UT) and Ferguson (R-NJ) introduced the Strategies to Address Antimicrobial Resistance Act (`STAAR Act_),[146] which aimed to impede antibiotic resistance by funding data compilation and stewardship programs.[147] The bill received enthusiastic support from the IDSA and other scientific organizations, but has not been passed despite the multiple re-introductions of the bill.[148] Also in 2007, Senator Bernie Sanders (I-VT) introduced the Medical Innovation Prize Act.[149] The bill proposed that the pharmaceutical manufacturer receive a cash reward for developing a medical innovation, rather than a traditional patent right.[150] Cash rewards, unlike patent rights, incentivize the innovation and conservation of antibiotics because pharmaceutical companies are not required to capitalize on sales during the drug˘s patented years.[151] Thus, a cash prize creates an inducement for antibiotic development that is otherwise missing in the existing price/volume landscape of the pharmaceutical industry. Again, this bill did not gain popularity and Congress failed to pass the bill.[152]

Two years later, in 2009, Representative Slaughter (D-NY), the only microbiologist in Congress,[153] reintroduced the Preservation of Antibiotics for Medical Treatment Act (PAMTA), which was previously introduced in 2007 and aimed to eliminate the use of subtherapeutic doses of antibiotics in livestock feed.[154] The bill sought to reduce the use of

144. Id. at 232.

145. Biodefense and Pandemic Vaccine and Drug Development Act of 2006, S. 2564, 109th Cong. (2006); Schulman, supra note 142, at 232 (explaining that the Biodefense and Pandemic Vaccine and Drug Development Act of 2006 is aimed at strengthening countermeasures against outbreaks of illness that are deliberate, accidental, and/or natural).

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

147. Fox, supra note 29, at 49.

148. Strategies to Address Antimicrobial Resistance Act, S. 2313, 110th Cong. (2007); Strategies to Address Antimicrobial Resistance Act, H.R. 2400, 111th Cong. (2009); Fox, supra note 29, at 49˘50.

149. Medical Innovation Prize Act of 2007, S. 2210, 110th Cong. (2007).

150. S. 2210 í 2.

151. James Love, Prizes, Not Prices, to Stimulate Antibiotic R&D, SCIDEV.NET (Mar. 26, 2008), http://www.scidev.net/global/health/opinion/prizes-not-prices-to-stimulate-antibiotic-r-d-.html.

152. Schulman, supra note 142, at 233.

153. Helena Bottemiller, Rep. Slaughter Reintroduces PAMTA, Criticizes FDA Strategy for Tackling Antibiotic Resistance, FOOD SAFETY NEWS (Mar. 15, 2013), http://www.foodsafetynews.com/2013/03/rep-slaughter-reintroduces-pamta-criticizes-fdas-strategy-for-tackling-antibiotic-resistance/#.WAUGPOgrLXQ.

154. Preservation of Antibiotics for Medical Treatment Act of 2009, H.R. 1549, 111th Cong. (2009); Fox, supra note 29, at 50.

antibiotics in livestock by amending the FD&C Act to require animal drug manufacturers to demonstrate that `no harm to human health will be caused due to the development of antimicrobial resistance attributable to certain uses of that particular drug._[155] Representative Slaughter re-introduced PAMTA[156] in 2013 and 2015 which, again, was proven futile.[157]

In 2011, Representative Phil Gingrey, M.D. (R-GA) introduced the Generating Antibiotics Incentives Now (GAIN) Act.[158] The GAIN Act sought to reform the patent system by granting an additional five years of market exclusivity for `qualified infectious disease products._[159] At last, the GAIN Act˘s provisions were successful and signed into law in July 2012 by President Obama as part of the Food and Drug Administration Safety and Innovation Act.[160] Only four antibiotics have become available the in U.S. market with this designation as of December 29, 2014.[161] However, critics such as Kevin Outterson caution that efficacy of this law should not be overstated, warning that `qualifying infectious disease product designations should not be interpreted as evidence of accelerated antibiotic development._[162]

In December 2013, Phil Gingrey (R-GA) and Gene Green (D-TX) introduced the Antibiotic Development to Advance Patient Treatment (ADAPT) Act.[163] The ADAPT Act made it quicker and less expensive for a pharmaceutical company to place an antibiotic drug on the market[164] by amending the FD&C Act to create a pathway for the prompt approval of antibacterial drugs intended to treat serious or life-threatening diseases and conditions.[165] The ADAPT Act also requires additional labeling, stating:

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155. AM. VETERINARY MED. ASSOC., PRESERVATION OF ANTIBIOTICS FOR MEDICAL TREATMENT ACT (PAMTA) ´ H.R. 1552 (2016), https://www.avma.org/Advocacy/National/Congress/Documents/IB_PAMTA_2016.pdf; Preservation of Antibiotics for Medical Treatment Act of 2015, H.R. 1552, 114th Cong. í 4 (2015).

156. Preservation of Antibiotics for Medical Treatment Act of 2013, H.R. 1150, 113th Cong. (2013).

157. GOVTRACK, H.R. 1150 (113th): Preservation of Antibiotics for Medical Treatment Act of 2013, https://www.govtrack.us/congress/bills/113/hr1150 (last visited Jan. 27, 2017).

158. Generating Antibiotic Incentives Now Act of 2011, H.R. 2182, 112th Cong. (2011).

159. GAIN: How a New Law Is Stimulating the Development of Antibiotics, PEW CHARITABLE TRUSTS (Nov. 7, 2013), http://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics.

160. Id.

161. Outterson, supra note 64, at 281.

162. Id.

163. Antibiotic Development to Advance Patient Treatment Act of 2013, H.R. 3742, 113th Cong. (2013).

164. :ADAPT˘: A Regulatory Pathway to Develop Antibiotics and Fight Drug Resistant Infections, PEW CHARITABLE TRUSTS (Jan. 29, 2014), http://www.pewtrusts.org/en/research-and-analysis/q-and-a/2014/01/29/adapt-a-regulatory-pathway-to-develop-antibiotics-and-fight-drug-resistant-infections.

165. Access to Marketplace Insurance Act, H.R. 3742, 114th Cong. (2015).

`This drug is indicated for use in a limited and specific population of patients._[166] The ADAPT Act, which was never passed into law, also sought to strengthen resistance monitoring by the CDC by ensuring that up-to-date and cutting-edge data was available to the government, as well as to healthcare professionals.[167]

Most recently, in December 2014, Senators Orrin Hatch (R-UT) and Michael Bennet (D-CO) re-introduced legislation to accelerate the approval of new antibiotics.[168] The Promise for Antibiotics and Therapeutics for Health (PATH) Act sought to establish a new drug approval pathway in order to encourage development and streamline the process of antibiotic drugs in the FDA for an `identifiable, limited patient population upon determining that the drug treats a serious or life-threatening condition and addresses an unmet need._[169] In addition, the PATH Act requires a special designation on antibiotic drug labels to indicate their intended use in limited, high-risk populations.[170] The legislation takes a creative approach by emphasizing the importance of such research, particularly veterans who have encountered antibiotic-resistant bacteria while overseas.[171] The legislation received support from IDSA, which emphasized that, `the PATH Act will not only help spur the development of urgently needed new antibiotics . . . [it] will also help ensure these precious new drugs are used appropriately to limit the development of resistance._[172]

As of November 2016, Congress has yet to act upon the PATH Act.[173] It is too soon to tell, but Congress˘ track record indicates general apathy on the issue.[174] This apathy, coupled with lobbying challenges by both the pharmaceutical and agriculture industries, makes the bill˘s passage into law seem unlikely. However, with the Obama Administration˘s recent push for antibiotic resistance efforts, the time is ripe for change.[175] Passing

166. Outterson, supra note 64, at 280.

167. H.R. 3742 í 2.

168. Promise for Antibiotics and Therapeutics for Health Act, S. 2996, 113th Cong. (2014).

169. Bennet, Hatch Reintroduce PATH Act to Streamline Approval of Antibiotics, SEN. MICHAEL BENNET (Jan. 16, 2015), https://www.bennet.senate.gov/?p=release&id=3229.

170. Id.

171. Id.

172. Id.

173. See Promise for Antibiotics and Therapeutics for Health Act, S. 185, 114th Cong. (2015).

174. Fox, supra note 29, at 48, 51.

175. See Press Release, Office of the Press Sec˘y, The White House, FACT SHEET: Obama Administration Releases National Action Plan to Combat Antibiotic-Resistant Bacteria (Mar. 27, 2015), https://www.whitehouse.gov/the-press-office/2015/03/27/fact-sheet-obama-administration-releases-national-action-plan-combat-ant (releasing a plan for federal departments and agencies to combat the rise of antibiotic-resistant bacteria); see

the PATH Act would be a positive step to incentivize the development of antibiotics through reducing the burden of the clinical trial process, as well as to encourage conservation through labeling changes.[176] Congress would be wise to act expediently to pass the PATH Act as a first step to addressing both conservation and innovation in the field of antibiotics. Understanding Congress˘ limitations to granting legislation to curb antibiotic-resistance, Part IV proposes working creatively within the existing statutory framework to address both pharmaceutical innovation and antibiotic conservation in the field of antibiotics through the Orphan Drug Act (ODA) and CSA.

IV. USING EXISTING LEGISLATION TO PROMOTE ANTIBIOTIC INNOVATION

As demonstrated above, Congress has tried and failed again to implement regulations to effectively conserve antibiotic drugs and incentivize the development of new classes of antibiotic therapies. An alternative to implementing new law is to work creatively within the existing statutory framework to address both conservation and innovation in the field of antibiotics. Regarding innovation, the ODA may be used to encourage pharmaceutical manufacturers to invest in R&D in the field of antibiotics.[177] When it comes to conservation, the CSA may be creatively interpreted to monitor the distribution of antibiotics.[178]

A. The Orphan Drug Act

The ODA was passed in 1983 to encourage research for the treatment of rare conditions affecting less than 200,000 people in the United States.[179] Companies may also apply for an orphan designation without hitting this benchmark if they can establish that developing a drug for the condition is otherwise economically disadvantageous because there is `no reasonable expectation_ that sales could support development of the drug in the United States.[180] The ODA is a form of `federal cost-sharing_ for qualified research projects that also aims to lessen the cost and regulatory burden of the clinical trial process.[181] The ODA encourages pharmaceutical

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generally NATIONAL STRATEGY, supra note 8 (outlining the goals of the United States Government to reduce antibiotic resistant bacteria and protect the public from related threats).

176. See S. 2996.

177. See Kesselheim & Outterson, supra note 83, at 139 (explaining that the ODA can decrease up-front costs of R&D through tax incentives and research grants).

178. See Geltman, supra note 135, at 123 (conjecturing that scheduling under the CSA might be qualified because there is evidence that some antibiotic misuse is psychological).

179. 21 U.S.C. í 360ee(b)(2) (2006).

180. Id.

181. Kesselheim & Outterson, supra note 83, at 139.

manufacturers by providing federal funding for grants and contracts to perform clinical trials for orphan products, offering a research tax credit of fifty percent of clinical testing costs, and guaranteeing a seven year market exclusivity period from the date of marketing approval.[182] From 1983 to 2010, over 350 therapies entered the United States market with orphan designations.[183] While the ODA has been most effective in oncology drugs, it has been used for products that target infectious diseases as well.[184]

The ODA helps address the issue that arises from the price/volume model of the pharmaceutical industry, which would otherwise avert pharmaceutical companies from investing in R&D for rare diseases.[185] The ODA has already incentivized pharmaceutical manufacturers to pursue antibiotic R&D by decreasing the upfront R&D costs.[186] Indeed, the FDAAA of 2007 financially supported a conference to determine when ODA incentives for certain antibiotics developed to treat infectious diseases due to antibiotic-resistant bacteria.[187] There has since been an increase in antibiotic therapies with Orphan Drug designation without any significant change to the law.[188] While the ODA incentivizes innovation, it does not address the issue of antibiotic conservation.[189] Thus, the ODA should be looked at as just one piece of the puzzle, rather than a cure-all to solve antibiotic resistance.[190]

B. The Controlled Substances Act

The CSA is the federal government˘s primary means of controlling the supply of drugs.[191] The statute allows the federal government to control access and use of certain drugs, and it can even eliminate classes of drugs

182. Id. at 140.

183. Id.

184. Id. at 141.

185. See Henry A. Waxman, The History and Development of the Orphan Drug Act, in ORPHAN DISEASES & ORPHAN DRUGS 135, 139˘40 (1986).

186. Enrique Seoane-Vazquez et al., Incentives for Orphan Drug Research and Development in the United States, 3 ORPHANET J. OF RARE DISEASES 1, 5 (Dec. 16, 2008), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631478/pdf/1750-1172-3-33.pdf.

187. Food and Drug Admin. Amendments Act of 2007, Pub. L. No. 110-85 í 1112, 121 Stat. 976 (2007).

188. Kesselheim & Outterson, supra note 83, at 140˘141 (`In the first half of 2008, two of the sixty-one new orphan drug designations related to antibiotics. For example, one of the orphan drug designations was granted to Mpex Pharmaceuticals for an IDSA-designated priority pathogen, specifically for the :[t]reatment of pulmonary infections due to Pseudomonas aeruginosa and other bacteria in cystic fibrosis patients.˘_).

189. Id. at 142.

190. See id.

191. Thomas M. Quinn & Gerald T. McLaughlin, The Evolution of Federal Drug Control Legislation, 22 CATH. U. L. REV. 586, 605 (1973) (explaining that the enactment of the CSA repealed all prior federal drug legislation and created a comprehensive scheme for drug control in one statute).

from the market.[192] One must register with the Drug Enforcement Agency (DEA) to prescribe or dispense a scheduled drug.[193] All scheduled drugs require the prescriber and dispenser to keep accurate and detailed records of their transactions.[194] In addition, Schedule I and II drug prescriptions require each order to be placed on a triplicate, with one copy forwarded to the DEA.[195] The CSA also provides disincentives to physicians for drug over-prescription in the form of penalties, ranging from a $100,000¯250,000 fine to up to one year in prison for first-time offenders.[196]

The CSA can theoretically incorporate antibiotics as a Schedule V controlled substance.[197] The Department of Health and Human Services (HHS) Secretary and the Attorney General (AG) (or the DEA with the AG˘s delegated authority) share drug-scheduling authority.[198] When scheduling a drug, the HHS makes medical judgments[199] and scientific determinations about a specific drug product, and the AG promulgates the rules relating to the registration and control of the `efficient execution of his functions._[200] Eight factors are considered in determining whether the scheduling should be authorized: (1) the actual or potential abuse of the drug; (2) the scientific evidence of its pharmacological effect; (3) the state of current scientific knowledge; (4) the history and current pattern of abuse of the drug; (5) the scope, duration, and significance of the abuse; (6) the risks to the public health; (7) the psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled under this subchapter.[201]

The CSA establishes three elements for Schedule V drugs: (1) the drug has a low potential for abuse relative to the drugs or other substances in schedule IV; (2) the drug has a currently accepted medical use in treatment in the United States; and (3) abuse of the drug may lead to limited

192. 21 U.S.C. í 812 (2012).

193. NIELSEN, supra note 128, at 67.

194. BRIAN T. YEH, CONG. RESEARCH SERV., RL34635, THE CONTROLLED SUBSTANCES ACT: REGULATORY REQUIREMENTS 2 (2012).

195. Id. at 97.

196. BRIAN T. YEH, CONG. RESEARCH SERV., RL30722, DRUG OFFENSES: MAXIMUM FINES AND TERMS OF IMPRISONMENT FOR VIOLATIONS OF THE FEDERAL CONTROLLED SUBSTANCES ACT AND RELATED LAWS 6 (2015).

197. Scott B. Markow, Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse, 87 GEO. L.J. 531, 542 (1998) (`The Attorney General may be able to schedule antibiotics based on potential for abuse by prescribers and the risk that they pose to the public health._).

198. Gonzales v. Oregon, 546 U.S. 243, 265 (2006).

199. Id. at 265.

200. Id. at 259.

201. 21 U.S.C. í 811(c)(1)(7) (2015).

physical dependence or psychological dependence relative to the drugs in Schedule IV.[202] Other Schedule V drugs include antidiarrheal, antitussive, and analgesic medications.[203] Antibiotic drugs could fall under the purview of the CSA if the HHS Secretary established scientific findings to demonstrate that misuse or abuse of antibiotics constitutes a threat to public health, thereby justifying federal control of the drug and satisfying the first element of a Schedule V drug under the CSA.[204] This would be an innovative use of the CSA because the purported abuse not only harms the individual, but the greater concern is one of public health. As noted above, the CDC reports that up to fifty percent of all antibiotics prescribed are unnecessary, giving rise to the looming public health threat of antibiotic resistance.[205]

To avoid penalties or liability through the over-prescription of antibiotics, doctors need only do what they are already supposed to do: prescribe antibiotics when it is medically necessary to do so.[206] However, critics of controlled substance laws suggest that they deter doctors from providing appropriate medication.[207] Such efforts may threaten physician autonomy by interfering with the practice of medicine and run the risk of a chilling effect on the appropriate prescription of antibiotics to patients who actually need them, thereby adversely affecting patient outcomes.[208] Still, in clinical practice, scheduling a drug does not necessarily lead to limiting access to patients who need them.[209] Rather, the system merely adds a system of checks on the prescribing physician to affirm that the drug is clinically necessary before prescribing it.[210] Further, the CSA does not address the issue of antibiotic innovation; it is just one potential piece in a

202. 21 U.S.C. í 812(b)(5) (2012).

203. U.S. DRUG ENFORCEMENT ADMIN., Drug Scheduling, http://www.dea.gov/druginfo/ds.shtml (last visited Nov. 14, 2016).

204. See 21 U.S.C. í 811(c)(6) (2015) (noting that the danger of the drug to the public health is a factor that should be taken into account when making scheduling decisions).

205. See CTR. FOR DISEASE CONTROL & PREVENTION, Antibiotic Resistance Questions & Answers, http://www.cdc.gov/getsmart/community/about/antibiotic-resistance-faqs.html (last updated Apr. 17, 2015) (noting that the unnecessary overuse drives resistance).

206. Markow, supra note 197, at 542 (discussing how the law places no limits on when a particular legend drug may be prescribed).

207. See The Supreme Court ´ Leading Cases: Gonzales v. Oregon, 120 HARV. L. REV. 361, 365 (2006) (discussing how the CSA was not intended to regulate medical practice and was meant to prevent drug abuse).

208. See Fox, supra note 29, at 59¯60; see also Evans, supra note 109, at 514 (limiting physician prescription practices may inhibit physicians from prescribing antibiotics to patients who could benefit from the antibiotics).

209. See Fox, supra note 29, at 59 (discussing a REMS restriction on antibiotics that are in need of preservation).

210. See id.

broader and more comprehensive scheme to effectively combat antibiotic resistance.[211]

V. A COMPREHENSIVE STATUTORY RESPONSE TO ANTIBIOTIC RESISTANCE

The enormous public health threat of antibiotic resistance requires more than just `feel good_ action without any statutory or regulatory teeth. It necessitates sweeping regulations to reduce the overuse, curb misuse, and incentivize the development novel antibiotic drugs. Passing new statutory and regulatory guidelines will take time, coordination, and perseverance. Until a new regulatory regime surrounding antibiotics is established, it is essential to work creatively within the existing statutory frameworks to curb resistance. These efforts should focus on both the conservation of antibiotic drugs and the innovation of new antibiotic therapies.

In regards to antibiotic innovation, Congress should, first and foremost, adopt the PATH Act to establish a new drug approval pathway within the FDA.[212] The PATH Act would incentivize antibiotic development by lessening the burden of the time-consuming and expensive clinical trial process through a new establishing regulatory approval pathway. Until Congress acts to pass new legislation, pharmaceutical companies should take advantage of the existing ODA when developing novel antibiotics to benefit from the federal funding grants, research tax credits, and guaranteed market exclusivity period. These measures will promote the development of novel antibiotic therapies, which have otherwise proven to be unprofitable in the price/volume driven pharmaceutical landscape.

On the antibiotic conservation front, the FDA should use its authority to implement a REMS restriction for novel antibiotic drugs to reduce misuse and over-prescribing where antibiotics are not clinically necessary. Until such time that the FDA acts, the HHS Secretary and the AG may act to classify certain antibiotics as Schedule V Controlled Substances under the existing CSA, allowing for DEA enforcement via penalties, or liability for misuse or overuse of antibiotics where they are deemed not clinically necessary. Orchestration amongst these federal actors will necessarily be complex, but it will allow for the most detailed and comprehensive approach to combat the diverse causes of antibiotic resistance. These combined efforts could provide a robust and multifaceted federal approach to address antibiotic resistance and protect the public health.

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211. See id.

212. Chris Dall, Health Groups Urge Senate to Pass Antibiotics Bill, U. MINN. CTR. FOR INFECTIOUS DISEASE RES. & POL`Y (Sept. 6, 2016), http://www.cidrap.umn.edu/news-perspective/2016/09/health-groups-urge-senate-pass-antibiotics-bill.