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Off-Label Promotion, the First Amendment, and Practically Addressing Antibiotic Resistance

Erin LaMontagne

OFF-LABEL PROMOTION, THE FIRST AMENDMENT, AND PRACTICALLY ADDRESSING ANTIBIOTIC RESISTANCE

INTRODUCTION

For many people in the United States today, fatal bacterial infections reside in our collective consciousness as mere ghosts of history—problems of the past. This cultural amnesia is primarily due to the discovery and widespread use of antibiotics.[1] But, the routine, copious, and often unnecessary use of antibiotics has brought our species to the threshold of a modern medical crisis: a return to the pre-antibiotic past caused by antibiotic resistance.[2]

In recent years, deaths caused by previously treatable bacterial infections have been growing.[3] According to the Centers for Disease Control and Prevention (CDC), over twenty-thousand people die each year from these infections,[4] and that number is on the rise. One

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1. Infectious Diseases Soc'y of Am., *Facts about Antibiotic Resistance*, IDSOCIETY.ORG, http://www.idsociety.org/AR_Facts/#sthash.KvkrBQ9j.dpuf (last visited Apr. 26, 2015).

2. *See* discussion *infra* Part I.

3. Andrew Pollack, *Rising Threat of Infections Unfazed by Antibiotics*, NYTIMES.COM, http://www.nytimes.com/2010/02/27/business/27germ.html?_r=0 (Feb. 26, 2010). Recently, in 2015, an outbreak of an antibiotic resistant bacteria, carbapenem-resistant *Enterobacteriaceae* or "CRE" (a bacteria commonly found in the digestive tract), occurred at UCLA's Ronald Reagan Medical Center in California. *See* Jordan Rau, *UCLA Outbreak Highlights Challenge of Curbing Infections*, NPR.ORG (published Feb. 20, 2015, 10:09 AM), *available at* http://www.npr.org/blogs/health/2015/02/20/387743352/ucla-outbreak-highlights-challenge-of-curbing-infections. Two patients died and over 100 more became ill as a result of the outbreak. *See id.* "CRE is one of three kinds of infectious agents that the Centers for Disease Control and Prevention categorized as the drug-resistant threats that require the most urgent monitoring and prevention. CRE bacteria are resistant to almost all antibiotics, including carbapenems, which doctors often deploy as a last resort. The remaining treatments are often toxic." *Id.*

4. *See* Ctrs. for Disease Control & Prevention, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 14 (2013),

organism, methicillin-resistant *Staphylococus Aures* (MRSA), kills more Americans every year than emphysema, HIV/AIDS, Parkinson's disease, and homicide combined.[5] This phenomenon is called antibiotic resistance; the cause of this alarming trend is multifaceted and complex.[6] Misuse and overuse of antibiotics by physicians coupled with a lag in new drug development combine to create a perfect storm for antibiotic resistance,[7] which is a natural consequence of the use of antibiotics.[8] The combination of these factors also presents potential problems for long-term public health solutions. To properly and practically address this public health emergency, all causes of misuse and overuse of antibiotics must be addressed.

The discovery of antibiotics fundamentally transformed healthcare delivery around the world.[9] Today, patient care depends on actors other than physicians. Specifically concerning the treatment of bacterial infections, patient care relies on two essential non-physician actors: (1) pharmaceutical companies that develop antibiotics; and (2) the federal government that regulates the drug-market. As the use of antibiotics has become a cornerstone of our modern medical practice, the roles and responsibilities of these actors in responding to antibiotic resistance have become irreversibly intertwined.

Pharmaceutical companies research, develop, and market new drugs directly to physicians, including antibiotics. These activities are closely regulated by the Food & Drug Administration (FDA); the government agency "charged with protecting consumers from unsafe and fraudulent [drugs]."[10] The FDA reviews and approves a drug's

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http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf, at 11 [hereinafter *CDC Threat Report*].

5. Infectious Disease Soc'y of Am., *Combating Antimicrobial Resistance: Policy Recommendations to Save Lives*, 52 (Supp. 5) Clin. Infectious Diseases S397-S428, S397 (2011), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3738230/.

6. Richard S. Savert, *In Tepid Defense of Population Health: Physicians and Antibiotic Resistance*, 34 AM J. L. & MED. 431, 433 (2008).

7. *See* discussion *infra* Part I.

8. *See* discussion *infra* Part I.A.

9. *Facts about Antibiotic Resistance*, *supra* note 1.

10. Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 647 (2014).

usage, safety, and efficacy information and communicates its findings to potential consumers through the official drug-label.[11] Additionally, the official drug-label contains only the specific uses reviewed and approved by the FDA.[12] However, physicians are not strictly bound by drug labels when prescribing a drug.[13] Physicians may legally use their medical judgment to prescribe a drug for off-label uses, or dosages, because the FDA does not regulate how physicians practice medicine.[14] However, off-label prescribing is distinguishable from off-label promotion by pharmaceutical companies.[15] Off-label promotion raises many controversial questions.[16] Aggressive off-label promotion of antibiotics contributes to the public health problem of antibiotic resistance,[17] and is therefore subject to FDA regulation. Inappropriate prescription of antibiotics to patients by physicians drives the development of antibiotic resistance.[18] In order for physicians to make accurate medical judgments about a drug, physicians must be given complete and unbiased information about the drug's proper uses. However, physicians are often busy and, so, rely on pharmaceutical marketers to provide them with information about a new drug.[19] Keenly aware of this reliance, pharmaceutical sales representatives often use off-label promotion to encourage physicians to prescribe a particular drug more often than may be necessary.[20] This practice is particularly troubling when considered in the context of promoting new antibiotics to physicians.

Part I of this comment briefly describes what antibiotic resistance is and how it has become a public health emergency. Part II details

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11. Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial* Speech, 37 AM. J. L. & MED. 225, 225 (2011).

12. *See* discussion *infra* Part II.A.

13. Greene, *supra* note 10, at 647.

14. *Id.*

15. *Id.*

16. *Id.* ("The FDA discourages off-label promotion because the practice allows manufactures to evade scientific evaluation of safety and efficacy for these uses.").

17. *See* discussion *infra* Part I.

18. *See* discussion *infra* Part I.C.

19. *See* discussion *infra* Part III.

20. *See* discussion *infra* Part III.

the roles of and relationships between pharmaceutical companies, the FDA, and physicians in the context of antibiotics. Part III outlines the effect of pharmaceutical promotion, particularly off-label statements, on physicians' prescribing behaviors. Part IV explains why the current legislative approach to addressing antibiotic resistance, by encouraging the development of new antibiotics, is incomplete without addressing the problems off-label promotion presents. Finally, Part V describes why the FDA should be allowed to regulate the off-label promotion of new antibiotics, and how doing so survives First Amendment scrutiny. Given the unique public health threat posed by antibiotic resistance, the FDA should regulate aggressive and inappropriate off-label promotion of new antibiotics to ensure the progress of new antibiotic development is not undone.

I. THE PUBLIC HEALTH EMERGENCY OF ANTIBIOTIC RESISTANCE FINDS ITS CAUSE IN MISUSE AND OVERUSE OF ANTIBIOTICS

Antibiotic resistance is a predictable phenomenon that has rapidly become a public health emergency due to, among other factors, the misuse and overuse of antibiotics.[21] This section provides a foundational description of: (1) what antibiotics are and how antibiotic resistance occurs; (2) why antibiotic resistance is a public health emergency that threatens the practice of modern medicine; and (3) how misuse and overuse of antibiotics, and a lag in new antibiotic development, combine to create a perfect storm for the rapid spread of antibiotic resistance.

A. Antibiotics & Antibiotic Resistance

Since being introduced into mainstream medicine in the 1940s, antibiotics have become an essential cornerstone of modern

21. *See* William M. Sage & David A. Hyman, *Combating Antimicrobial Resistance: Regulatory Strategies and Institutional Capacity*, 84 TUL. L. REV. 781, 790 (2010). There are several other factors that contribute to antibiotic resistance not addressed in this comment, such as: (1) containment of resistance organisms to prevent their proliferation; (2) the use of antibiotics in food production; and (3) prevention of infection. *Id.* at 792–94.

medicine.[22] Antibiotics are essential for a wide variety of medical procedures including routine surgical procedures to organ transplants to treatment of cancer and HIV.[23] However, according to the CDC "these drugs have been used so widely and for so long that the [bacteria] the antibiotics are designed to kill have adapted to [the antibiotics], making the drugs less effective."[24] This phenomenon is known as antibiotic resistance.[25]

"Antibiotic" is a general term that describes a class of drugs, chemicals, and substances that can kill, or stop the growth of, bacteria.[26] Antibiotics kill or inhibit the growth of different bacteria by targeting certain processes within the bacteria that make the bacteria unable to survive or reproduce.[27] Antibiotics can either be produced naturally by living organisms or developed in a laboratory by combining different chemical compounds.[28] Additionally, there are different classes of antibiotics, distinguishable from each other based on how they kill or inhibit the growth of bacteria: also known as an antibiotic's "mode of action."[29] "Narrow-spectrum" antibiotics

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22. Ctrs. for Disease Control & Prevention, *About Antimicrobial Resistance: A Brief Overview*, CDC.GOV, http://www.cdc.gov/drugresistance/about.html (last updated Sept.16, 2013) [hereinafter *CDC About Antimicrobial Resistance*].

23. Cesar A. Arias & Barbara E. Murray, *Resistant Bugs in the 21st-Century—A Clinical Super-Challenge*, 360 NEW. ENG. J. MED 439 (2009), *available at* http://www.nejm.org/doi/full/10.1056/NEJMp0804651 (last visited Apr. 26, 2015).

24. *CDC About Antimicrobial Resistance*, *supra* note 22.

25. *Id.*

26. *Id.*

27. *See* Hiroshi Yoneyama & Ryoicihi Katsumata, *Antibiotic Resistance in Bacteria and Its Future for Novel Antibiotic Development*, 70(5) Biosci., Biotech., & Biochem. 1060, 1060–75, 1060–61 (2006) (classic targets for antibiotics are: (1) cell wall biosynthesis (production/creation of something from a living organism) pathways; (2) protein biosynthesis pathways; (3) DNA and RNA biosynthesis pathways; and (4) folate (or folic acid) biosynthesis).

28. Ctrs. for Disease Control & Prevention, *Get Smart: Know When Antibiotics Work*, CDC.GOV, http://www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html#define-antibiotics (last updated Dec. 18, 2013) [hereinafter *CDC When Antibiotics Work*] (The first antibiotic, penicillin, was discovered using mold by Alexander Flemming in 1928.).

29. Compound Interest, *A Brief Overview of Classes of Antibiotics*, COMPOUNDCHEM.COM, http://www.compoundchem.com/2014/09/08/antibiotics/ (last visited Dec 28, 2014). For example, penicillin belongs to a class of antibiotics

describe classes of antibiotics that target specific reactions in certain species of bacteria; "broad-spectrum" antibiotics describes classes of antibiotics that effect general features within bacteria and, therefore, affect a wider range of bacteria.[30] However, "[b]acteria are any of a very large [and diverse] group of single-celled microorganisms that display a wide range of metabolic types, geometric shapes and environmental habitats."[31] Because of this immense diversity, no one antibiotic or class of antibiotics works on all types of bacteria.[32]

Antibiotic resistance "is the result of [bacteria] changing in ways that reduce or eliminate the effectiveness of [antibiotics] to cure or prevent infections."[33] Bacteria can develop resistance to a specific antibiotic or to an entire class of antibiotics.[34] The mere use of antibiotics can create antibiotic resistance.[35] This is not surprising, because bacteria's development of antibiotic resistance is a predictable result of a natural selection[36] occurring at the microbial level.[37] After many generations, the process of natural selection produces bacteria

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called Beta-Lactums, which work by inhibiting the bacteria from making their cell wall causing them to die. *See* Compound Interest, *Different Classes of Antibiotics: An Overview*, COUMPOUNDCHEM.COM, http://www.compoundchem.com/wp-content/uploads/2014/09/Major-Classes-of-Antibiotics-Summary-v2.png (last visited Apr. 27, 2015) (chart depicting different classes of antibiotics, when they were discovered, examples, and their modes of action).

30. Stephen Claydon, *Antibiotics*, SCIENCEAID.CO.UK, http://scienceaid.co.uk/biology/micro/antibiotics.html (last visited Dec. 28, 2014).

31. C. Michael Hogan, *Biodiversity: Bacteria*, EOEARTH.ORG, http://www.eoearth.org/view/article/150368/ (published Oct. 12, 2014 6:54 PM).

32. *See* Claydon, *supra* note 30.

33. *Id.* (defining "antibiotic" and "antimicrobial agent").

34. Sage & Hyman, *supra* note 21, at 788.

35. *CDC Threat Report*, *supra* note 4, at 14.

36. Natural selection is "[a] process in which some individuals have genetically-based traits that improve survival or reproduction and thus have more offspring surviving to reproductive age than other individuals." *Understanding Evolution*, EVOLUTION.BERKELEY.EDU, http://evolution.berkeley.edu/evosite/glossary/ glossary_browse.shtml (last visited May 5, 2015).

37. THE WORLD HEALTH ORG., *Antimicrobial Resistance*, WHO.INT, *available at* http://www.who.int/mediacentre/factsheets/fs194/en/ (last updated Apr. 2014) ("The evolution of resistant strains is a natural phenomenon that occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them.").

able to survive in an environment despite the presence of antibiotics.[38] This phenomenon is easily observed in bacteria, because bacteria reproduce very rapidly producing multiple generations in a single day.[39] Dramatic environmental changes often accelerate the process of natural selection.[40] When an environment changes and suddenly becomes hostile to an organism's survival, one of two things will happen: the organism will survive or the organism will die.[41] The more dramatic the change, the stronger the effect of natural selection will be on the organism.[42]

Bacterial cells outnumber human body cells by ten to one and make up about 1-3% of our total body mass.[43] Our bodies are ideal environments for bacteria, and we depend on many of these organisms to survive.[44] However, sometimes bacteria inside our bodies can make us sick.[45] This is when antibiotics enter the picture.[46] When an antibiotic enters the human body, it introduces a compound or

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38. Am. Museum of Nat. History, *Right Before Our Eyes*, AMNH.ORG, http://www.amnh.org/exhibitions/past-exhibitions/darwin/evolution-today/how-long-does-evolution-take/right-before-our-eyes (last visited Apr. 27, 2015).

39. *Id.*

40. Am. Museum of Nat. History, *Extinction or Opportunity?*, http://www.amnh.org/exhibitions/past-exhibitions/darwin/evolution-today/how-do-new-species-evolve/extinction-or-opportunity (last visited Apr. 27, 2015) (through a process called punctuated equilibrium).

41. *See id.*

42. *See* ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, *General Background About Antibiotic Resistance*, *available at* http://www.tufts.edu/med/apua/about_issue/about_antibioticres.shtml (last visited Dec. 28, 2014); *see also*, *More on Punctuated Equilibrium*, http://evolution.berkeley.edu/evosite/evo101/VIIA1bPunctuated.shtml (last visited Apr. 27, 2015) (the effect of natural selection is also referred to as "selection pressure").

43. *NIH Human Microbiome Project Defines Normal Bacterial Make-Up of the Body*, NIH.GOV (June 13, 2012), *available at* http://www.nih.gov/news/health/jun2012/nhgri-13.htm ("Genes carried by bacteria in the gastro-intestinal tract, for example, allow humans to digest foods and absorb nutrients that otherwise would be unavailable.").

44. *Id.*

45. *CDC About Antimicrobial Resistance*, *supra* note 22 (explaining bacteria and other microbes).

46. *CDC When Antibiotics Work*, *supra* note 28.

chemical hostile to the infectious bacteria's survival.[47] This drastically changes the body's environment and puts pressure on the bacteria to resist the effect of the antibiotic.[48] Bacteria that can survive in an environment containing the antibiotic live; the rest perish, leaving only the resistant bacteria behind.[49] The probability that an antibiotic will produce bacteria resistant to it depends on the strength of the antibiotic's selection pressure.[50] "Whether the antibiotic will have a strong selection [pressure] . . . depends on several factors, including the amount of the antibiotic used, the duration of use, the intervals between drug administration, the number of patients treated with the antibiotic, and the antibiotic's demographic influence."[51] Ultimately, one of modern medicine's most successful innovations has a potentially chilling side effect:

> [T]here is an antibiotic paradox—prescribing an antibiotic can have dual, contradictory effects as it combats the targeted bacteria while also [possibly] increasing selection pressures in the larger environment for bacterial strains that are resistant to that antibiotic, . . . jeopardizing the medication's effectiveness when used again for future health threats.[52]

B. Antibiotic Resistance Threatens Modern Medicine

Antibiotic resistance is a growing public health concern in the United States and around the world.[53] In 2013, the CDC published its

47. Savert, *supra* note 6, at 440.

48. *Id.*

49. ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, *supra* note 42.

50. "[Selection] Pressure—The influence exerted by some factor (such as an antibiotic) on natural selection to promote one group of organisms over another. In the case of antibiotic resistance, antibiotics cause a selective pressure by killing susceptible bacteria, allowing antibiotic-resistant bacteria to survive and multiply." ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS, *Glossary*, TUFTS.EDU, *available at* http://www.tufts.edu/med/apua/about_issue/glossary.shtml#sel (last visited Apr. 27, 2015); *see also* Savert, *supra* note 6, at 431, 439–40.

51. Savert, *supra* note 6, at 440.

52. *Id.* at 436 (internal quotations omitted).

53. Fed. Food & Drug Admin., *Combating Antibiotic Resistance*, *available at* http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm092810.htm#antibiotics (last updated Oct. 14, 2014).

first "Threat Report," which provides a "snapshot" of antibiotic resistance threat in the United States.[54] Alarmingly, the CDC found bacterial infections, long believed to be vanquished by modern medicine, are making a rapid comeback.[55] Additionally, the CDC reported that "[e]ach year in the United States, at least 2 million people acquire serious infection with bacteria that are resistant to one or more of the antibiotics designed to treat those infections . . . [and] at least 23,000 people die as a direct result."[56]

Antibiotic resistance also puts direct and indirect financial strains on an already overburdened healthcare system.[57] The CDC estimated that antibiotic resistance costs the U.S. economy $20 billion dollars in direct excess healthcare costs, and an additional $35 billion dollars in costs to society, including loss of productivity.[58] These avoidable excess costs arise from "prolonged and/or costlier treatments, [extended] hospital stays . . . additional doctors visits and health care use, and result in greater disability and death compared with [non-resistant antibiotic infections]."[59]

These trends are increasing at an alarming speed as antibiotic resistance becomes more prevalent.[60] "Antibiotics are among the most commonly prescribed drugs used in human medicine,"[61] but, antibiotic resistance threatens our ability to treat common disease and perform routine medical procedures.[62]

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54. *CDC Threat Report*, *supra* note 4, at 6.

55. For example, tuberculosis, typhoid fever, Group B Strep, gonorrhea, etc. CDC, *Biggest Threats*, CDC.GOV, http://www.cdc.gov/drugresistance/biggest_threats.html (last updated Sept. 16, 2014) (see full list of the eighteen biggest bacterial threats to the U.S.).

56. *CDC Threat Report*, *supra* note 4, at 11.

57. *Id.*

58. *Id.* (estimates represent the upper range of the economic cost calculations, in U.S. dollars).

59. *Id.*

60. Sage & Hyman, *supra* note 21, at 788.

61. *CDC Threat Report*, *supra* note 4, at 11.

62. *Antimicrobial Resistance*, *supra* note 37 ("New resistance mechanisms emerge and spread globally threatening our ability to treat common infectious diseases, resulting in death and disability of individuals who until recently could continue a normal course of life. Without effective anti-infective treatment, many standard medical treatments will fail or turn into very high risk procedures.").

C. The Three Factors Creating a Perfect Storm: Misuse, Overuse, and No New Drug Development

Several factors contribute to the increased speed of antibiotic resistance.[63] Specifically, the combination of three major factors—misuse, overuse, and the lack of new antibiotic development—creates a perfect storm for an antibiotic resistance threat.[64]

The "[r]epeated . . . improper uses of antibiotics are [the] primary causes of the increase in [antibiotic]-resistant bacteria."[65] Two forms of improper use are: misuse and overuse.[66] Misuse occurs when antibiotics are improperly prescribed or are not taken as prescribed.[67] It "generally arises from faulty individual [physician] decision making, typically caused by lack of information, cognitive misperceptions of risk and benefits, or some combination thereof."[68] Physicians most commonly misuse antibiotics by prescribing them when they are useless.[69] Antibiotics are specifically designed to kill bacteria but are completely ineffective against viruses.[70] Thus, when an antibiotic is prescribed to treat a viral infection—like a cold or the flu—it is useless, unnecessary, and could cause harmful side effects.[71] According to the CDC Threat Report, "up to 50% of all the antibiotics

63. Sage & Hyman, *supra* note 21, at 792–95.

64. *See generally id.*; *see also* Ctrs. for Disease Control & Prevention, *National Strategy to Combat Antibiotic Resistance*, CDC.GOV, *available at* http://www.cdc.gov/drugresistance/national-strategy/index.html (last updated Sept. 22, 2014).

65. *CDC When Antibiotics Work*, *supra* note 28.

66. Sage & Hyman, *supra* note 21, at 790. This comment does not directly address the other issues such as containment, prevention, and use in food and agriculture.

67. *Combating Antibiotic Resistance*, *supra* note 53.

68. Sage & Hyman, *supra* note 21, at 791.

69. *Id.*

70. *Combating Antibiotic Resistance*, *supra* note 53.

71. *Id.* at 2 (Using an antibiotic to treat a viral infection: "(1) will not cure the infection; (2) will not keep other individuals from catching the virus; (3) will not help a person feel better; (4) may cause unnecessary, harmful side effects; and (5) may contribute to the development of antibiotic resistance.").

prescribed . . . are not needed or are not optimally effective as prescribed."

Overuse occurs when "big-gun," or broad-spectrum, antibiotics are used to treat infections that could be treated with weaker, narrow-spectrum, antibiotics.[72] The overuse of broad-spectrum antibiotics creates a strong selection pressure for resistant organisms to develop quickly.[73] Still further, overuse creates a risk to current and future patients with rare and often life-threatening infections.[74]

The third factor that contributes to this public health emergency is the considerable slowdown of new antibiotic development.[75] According to the CDC, the FDA approved just eight new antibiotics between 2000 and 2010.[76] Additionally, no new classes of antibiotics have been developed in the past two decades.[77] This unfortunate trend is unsurprising, because antibiotic discovery and development have become more scientifically complex, expensive, and time-consuming as medicine has progressed.[78]

Combined, these three factors have created a global public health emergency.[79] According to the Infectious Disease Society of America "[we have] reached a critical point in treating infectious diseases: new

72. *Id.*

73. *Id.*

74. *Id.*

75. *CDC Threat Report*, *supra* note 4, at 44.

76. *Id.* at 45–46.

77. *Id.*

78. Brad Spellberg, *New Antibiotic Development: Barriers & Opportunities in 2012*, APUA NEWSLETTER, Vol. 30 No. 1 (Alliance for the Prudent Use of Antibiotics (APUA) Clinical Newsletter), *available at* http://www.tufts.edu/med/apua/news/news-newsletter-vol-30-no-1-2.shtml (last visited Nov. 9 2014).

79. The World Health Organization (WHO) recognizes that antibiotic resistance "is an increasingly serious threat to global public health that requires action across all government sectors and society. . . . [According to] WHO's 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill." *Antimicrobial Resistance*, *supra* note 37.

[antibiotics] are not being developed at anywhere near the pace necessary to keep ahead of the natural ability of bacteria to evolve and defend themselves against antibiotics."[80] This means "some of our most powerful and medically essential drugs, antibiotics, are becoming useless."[81]

II. PHYSICIANS, PHARMACEUTICAL COMPANIES, AND THE FDA ALL PLAY KEY AND INTERRELATED ROLES IN THE REALM OF ANTIBIOTICS

Three crucial actors play integrated and essential roles in addressing the problem of antibiotic resistance: (1) pharmaceutical companies; (2) the FDA; and (3) physicians. A comprehensive and effective long-term response to antibiotic resistance requires an understanding of how these actors interact and influence one another.[82]

A. Pharmaceutical Companies: Researching, Developing, Manufacturing, and Marketing New Antibiotics

The role of pharmaceutical companies is to research, develop, manufacture, and market antibiotics.[83] Notwithstanding the slight decline in market growth because of generic drugs,[84] the U.S. pharmaceutical market is "still the largest single pharmaceutical market [worldwide], generating [nearly] 329 billion U.S. dollars [in

80. *Facts about Antibiotic Resistance*, *supra* note 1.

81. *Id.*

82. Other important actors who are not addressed in this comment are: (1) monitoring and data collection agencies like the CDC or state health departments; (2) patients; and (3) educational institutions and groups for both physicians and the general public. *See* Sage & Hyman, *supra* note 21, at 785–87.

83. Int'l Trade Admin., *Pharmaceutical Industry Profile*, TRADE.GOV, *available at* http://www.ita.doc.gov/td/health/PharmaceuticalIndustryProfile2010.pdf (last visited Apr. 27, 2015) (The U.S. Census Bureau defines pharmaceutical companies as "companies engaged in researching, developing, manufacturing, and marking drugs . . . for [medical] use.").

84. *Id.* at 4.

2013] of revenue."[85] However, despite pharmaceutical companies' impressive size and market presence, they have been reluctant to participate in the development of new antibiotics.[86] This reluctance is unfortunate yet unsurprising, because antibiotic discovery and development has become: (1) more scientifically complex; (2) costly; and (3) time-consuming as medicine has progressed.[87]

First, the difficulty and expense of discovering new and novel antibiotics has substantially increased because the "low-hanging fruit [in antibiotic discovery] has already been picked."[88] Generally, antibiotics inhibit specific "targets" within a type, or types, of bacteria that either kill or inhibit the growth of those bacteria.[89] "According to Dr. Yoneyama and Dr. Katsumata, although a large number of antibiotics are used clinically, the variety of targets they inhibit is limited."[90] The main strategy of the pharmaceutical industry in developing antibiotics has been to modify existing antibiotics.[91] Over time, this approach has produced less successful results, because modified antibiotics do not meet society's demands for new antibiotics. However, compared to the average forty years required to develop a new structural class of antibiotics, modifying existing drugs is much easier than trying to discover a new target.[92] According to the Alliance for the Prudent Use of Antibiotics, each new generation of antibiotics raises the bar, and the cost, in terms of the resources necessary to discover and develop successive generations.[93]

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85. *Global Pharmaceutical Sales from 2011 to 2013, by region (in billion U.S. dollars)*, STATISTA.COM, http://www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region/ (last visited Apr. 26, 2015).

86. Spellberg, *supra* note 78.

87. *Id.*

88. *Id.*

89. *See* Yoneyama & Katsumata, *supra* note 27, at 1060–75.

90. *Id.* at 1061 ("The main classes of antibiotics inhibit four classical targets (Fig. 1): (i) cell wall biosynthesis; (ii) protein biosynthesis; (iii) DNA and RNA biosynthesis; and (iv) folate biosynthesis.").

91. *Id.* at 1067–68.

92. *Id.*

93. Spellberg, *supra* note 78.

Second, pharmaceutical companies face lengthy and expensive regulatory challenges.[94] The general drug approval process can be broken down into four general stages: (1) preclinical; (2) clinical; (3) NDA Approval; and (4) post-marketing.[95] Over a ten-year period, it took seventy-two candidate antibiotics to yield one FDA-approved product, whereas other pharmaceuticals required an average of only fifteen candidates to yield an FDA-approved product.[96] In 2013, for all drug development, pharmaceutical companies spent about $51.5 billion dollars on research and development costs alone.[97] Additionally, the average cost of the entire approval process for a new drug can exceed eighty million dollars.[98] In fact, according to the Alliance for the Prudent use of Antibiotics, "[s]everal companies have publicly stated . . . that given how difficult it is to get antibiotics approved by the FDA, they are considering simply abandoning the U.S. antibiotic market."[99]

Pharmaceutical companies may be willing to deal with the scientific and regulatory challenges if antibiotics were "blockbuster

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94. *Id.*

95. After a drug is developed and tested on animals during the pre-clinical stage, the pharmaceutical company submits an application to the FDA for approval. *See* Food & Drug Admin., *Drug Approval Process*, FDA.GOV, http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (last visited Apr. 27, 2015) (graphical representation of the basic drug approval process). The FDA reviews this application to determine if the drug and proposed trials are appropriate for human testing. *Id.* Once the FDA approves the application, the clinical stage begins, which consists of three phases of human testing. *Id.* After a drug reaches phase two of that process, the FDA meets to determine if the drug should continue to phase 3 testing, and after the clinical stage is complete the FDA reviews the information on the drug label, the manufacturing facility, and the marketing material. *Id.* After the FDA approves all of the, the drug is officially approved for the market place. *Id.*

96. Caitlin Forsyth, Comment, *Repairing the Antibiotic Pipeline: Can the GAIN Act do it?*, 9 WASH. J.L. TECH. & ARTS 1, 5 (2013).

97. Biopharmaceutical Research Indus., 2014 Profile, PHRMA.ORG, http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf (last visited Apr. 27, 2015) ("Key Facts").

98. Daniel B. Klein & Alexander Tabarrok, *The Drug Approval and Development Process*, THE INDEPENDENT INSTITUTE, http://www.fdareview.org/approval_process.shtml (last visited Apr. 27, 2015).

99. Spellberg, *supra* note 78.

drugs" that would allow companies to make a return on significant investments.[100] Unfortunately, most companies do not see such returns; by the time the FDA approves a candidate antibiotic and puts it on the market, a 20-year patent term is likely nearing its end.[101] These low reimbursement rates combined with increasing competition with generic drugs drive down the price of new antibiotics. This results in companies having trouble making profits.[102] For example, the current models of reimbursement for antibiotics, such as bundled rates used in hospitals, provide strong incentives for hospitals and physicians to prescribe low-cost generic antibiotics.[103] Ultimately, it is challenges like these that make pharmaceutical companies less willing to develop new antibiotics.[104]

B. The FDA: Ensuring Safety and Efficacy of Drugs Before They Enter the Market

The fundamental function of the FDA is to protect consumers from unsafe, ineffective, or fraudulent food and drugs.[105] This is achieved by requiring that all new drugs be tested, reviewed, and approved for safety, efficacy, and effectiveness before reaching the market.[106] Rather than give a new drug a general blanket approval, the FDA approves drugs for specific uses[107] that must be requested by

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100. *Id.*; *see also* Kevin Outterson, *New Business Models for Sustainable Antibiotics*, 15–16 (Centre on Global Health Security Working Grp., Papers, Paper No. 1, 2014), *available at* http://www.Chathamhouse.org/sites/files/chathamhouse/public/Research/Global%20Health/0214SustainableAntibiotics.pdf.

101. Outterson, *supra* note 100, at 7.

102. *Id.* at 15–16.

103. *Id.*

104. Spellberg, *supra* note 78; s*ee also* Outterson, *supra* note 100, at 15–16.

105. Greene, *supra* note 10, at 646.

106. Kesselheim, *supra* note 11, at 225.

107. "[V]aldecoxib (Bextra), a cyclooxygenase-2 inhibitor type of non-steroidal anti-inflammatory drug that, in 2001, was submitted to the FDA for approval as a treatment for pain associated with osteoarthritis, rheumatoid arthritis, menstrual cycle pain, and acute pain. The FDA approved the drug for only the first three indications, rejecting acute pain as an indication because of specific dangers identified in pre-marketing trials." *Id.* (example of specific use approval done by the FDA).

the manufacturer.[108] After an extensive review of the drug's information submitted by the manufactures, the FDA summarizes its approved findings in the official drug-label.[109] The label contains: (1) a summary of basic information about the drug; (2) the results from pre-FDA-approval studies; (3) the dosage information; (4) safety information and warnings; and (5) the effectiveness of the drug per its FDA-approved uses.[110]

The FDA's regulatory authority does not end after it approves a new drug and pens the official drug-label; the FDA also regulates how drugs are marketed to consumers.[111] Pharmaceutical companies must submit their promotional materials to the FDA for review to ensure the materials "accurately summarize the drug's [uses] and risks."[112] This process is vital because The Food Drug and Cosmetics Act ("FDCA") restricts misleading and unsubstantiated promotional claims.[113] The FDCA and the FDA require pre-market approval primarily because "post-market actions against misleading claims are incapable of protecting consumers from unsafe and ineffective products."[114]

The FDA classifies uses and promotional statements similar to, or the same as, the FDA's approved label as "on-label."[115] Any uses or promotional statements outside the four corners of the label are considered "off-label."[116] While neither the FDA nor the FDCA expressly prohibit off-label promotion, courts have interpreted statutory language to punish pharmaceutical sales representatives for "misbranding" by giving information about an off-label use to a

108. *Id.*

109. *Id.* at 232.

110. *Id.*

111. Greene, *supra* note 10, at 647 n1.

112. Kesselheim, *supra* note 11, at 239.

113. Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD DRUG L.J. 299, 300–01 (2003); *see also* 21 C.F.R §201.5 (Deering 2014).

114. Waxman, *supra* note 113, at 299.

115. Kesselheim, *supra* note 11, at 255.

116. *Id.*

physician with the intent that the drug be prescribed in such a way.[117] Similarly, from the FDA's perspective, advertising a drug for a use other than the drug's "intended use"[118] is evidence of objective intent to introduce that drug into the stream of commerce for an unapproved use; therefore, such conduct potentially qualifies as "misbranding" under the FDCA.[119]

C. Physicians are the Gatekeepers of Antibiotics

Physicians perform a critical role as gatekeepers for antibiotics.[120] Patients can only receive an antibiotic through a physician's prescription; therefore, physicians have substantial control over the volume of antibiotics being used in humans.[121] In fact, physicians are the primary consumers of antibiotics designed to treat human pathogens, and pharmaceutical companies spend large sums on marketing directly to them.[122] This is potentially concerning when considering new antibiotics because physicians often rely on promotional statements as a primary source of information about a new drug.[123] According to the CDC, lack of information causes up to half of the prescriptions for antibiotics in the United States being prescribed inappropriately.[124] In fact, the information that physicians receive from pharmaceutical sales-representatives is often geared more towards selling a drug to a physician rather than presenting

117. Greene, *supra* note 10, at 658–59.

118. *See* 21 C.F.R. § 201.128 (Deering 2015) ("intended uses" refers to the "objective intent of the persons legally responsible for the labeling of drugs" and objective intent may be shown "by labeling claims, advertising matter, or oral or written statements by such persons or their representatives").

119. *See* Greene, *supra* note 10, at 659 ("Because labeling requirements are construed in a very broad manner, including oral representations made by pharmaceutical representatives, a representative who gives information about off-label use to a doctor with the intent that the drug be distributed in commerce is misbranding the drug.").

120. Savert, *supra* note 6, at 446–47.

121. *Id.* at 434–35.

122. *See* discussion *infra* Part III.

123. *See* discussion *infra* Part III.

124. *CDC Threat Report*, *supra* note 4, at 11.

objective information about the drug's uses.[125] Therefore, this could lead to physicians having incomplete information about a new antibiotic and inappropriately prescribe that antibiotic more often as a result.[126] Because misuse and overuse are two key driving factors for antibiotic resistance, it is essential that physicians receive accurate and unbiased information so they can prescribe antibiotics prudently.[127]

Pharmaceutical marketing statements must be addressed to prevent the improper prescription of new antibiotics because these statements have a strong effect on physicians' prescribing behaviors.[128]

III. THE EFFECT OF MARKETING ON PHYSICIANS' PRESCRIBING BEHAVIORS AND ANTIBIOTIC RESISTANCE

Studies show that pharmaceutical marketing has a statistically significant influence on physicians' prescribing choices and habits.[129] Thus, direct-to-physician off-label marketing could potentially perpetuate misuse and overuse of new antibiotics.

Marketing is vital for pharmaceutical companies and represents a large portion of their expenditures.[130] In 2012, pharmaceutical marketing expenditures exceeded approximately $27 billion dollars.[131]

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125. Greene, *supra* note 10, at 702–03.

126. *See* discussion *infra* Part III.

127. Savert, *supra* note 6, at 436.

128. *See* discussion *infra* Part III.A.

129. Katherine T. Vukadin, *Failure-to-Warn: Facing Up to the Real Impact of Pharmaceutical Marketing on the Physician's Decision to Prescribe*, 50 TULSA L. REV. 75, 82 (2014) (citing Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 5 YALE J. HEALTH POL'Y L. & ETHICS 785, 809 (2005)).

130. *Id.* at 79.

131. The Pew Charitable Trust, *Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients*, PEWTRUSTS.ORG (published Nov. 11, 2013), http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients [hereinafter *Persuading the Prescribers*] (citing Cegedim Strategic Data, 2012 U.S. Pharmaceutical Company Promotion Spending (2013), SKAINFO.COM, http://www.skainfo.com/health_care_market_reports/2012_promotional_spending.pdf).

"Some estimate that pharmaceutical companies spend about two times as much money on marketing than they do on research and development."[132] Further, the pharmaceutical industry employs several marketing strategies designed to promote drug companies' products by influencing doctors' prescribing practices.[133] Several of these strategies involve building a relationship with the physician with the express objective to influence the physician's prescribing behavior. These strategies include: (1) free samples; (2) promotional mailings; (3) gifts; (4) face-to-face meetings with physicians; and (5) journal and web advertisements.[134] The pharmaceutical industry's most successful marketing strategy is "detailing." Detailing is where sales representatives meet with and market drugs and devices directly to physicians.[135] Each year, detailers, who are trained to influence the prescribing behavior of physicians, make about 115 million promotional visits to physicians' offices.[136]

Generally, physicians report they are not influenced by pharmaceutical sales representatives.[137] Indeed, "[p]hysicians themselves tend to report that contacts with pharmaceutical representatives have little to no effect on their prescribing behavior, although some believe that their colleagues' judgment may be affected."[138] However, "[e]mpirical evidence indicates that despite physicians' beliefs to the contrary, pharmaceutical marketing is effective in influencing physicians' actions, whether those actions result in requesting additions to a formulary, initiating use of a certain

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132. *Persuading the Prescribers*, *supra* note 131 ("[A]pproximately 24.4. percent of each revenue dollar is spend on marketing as opposed to 13.4 percent on research and development.") (citing Donald W. Light & Joel R. Lexchin, *Pharmaceutical research and development: what do we get for all that money?*, BMJ.COM (published Aug. 7, 2012), http://www.bmj.com/content/345/bmj.e4348).

133. *Persuading the Prescribers*, *supra* note 131; *see also* Vukadin, *supra* note 129, at 80.

134. *Persuading the Prescribers*, *supra* note 131

135. Vukadin, *supra* note 129, at 80 ("The pharmaceutical industry considers detailing . . . to be the most effective form of pharmaceutical marketing.").

136. *Id.* ("Pharmaceutical sales representatives pay about 115 million visits to 340,000 [physicians] each year.").

137. *Id.* at 80–81.

138. *Id.*

drug, or choosing to prescribe one drug over another."[139] In fact, one meta-analysis indicated a positive association with the number of marketing visits and the frequency the marketed drug is prescribed.[140] However, "[s]tudies do not show that an increase in pharmaceutical representative visits correspond with any increase at all in prescribing quality."[141]

Courts often assume that physicians can distinguish between a sales pitch and a presentation of reliable scientific data, but that assumption is not always accurate.[142] Although physicians are highly educated, it is difficult to verify off-label statements made by drug detailers, because such information is not publicly available for new drugs.[143] Additionally, busy physicians often do not have extra time to assess new drugs, or antibiotics, independently.[144] Thus, physicians rely on detailers' statements.[145]

Because "[t]he prevailing business model is to recoup pharmaceutical [research and development] investments through sales revenues above marginal cost during a period of patent-based exclusivity," pharmaceutical sales representatives aggressively market new drugs for both on and off-label to physicians during their detailing sessions.[146] "The FDA discourages off-label promotion of drugs because the practice allows [pharmaceutical companies] to evade scientific evaluation of safety and efficacy."[147] Despite the FDA's concerns, off-label marketing is not only common, but is seen

139. *Id.* at 81.

140. *Id.* at 82.

141. *Id.* at 84.

142. Greene, *supra* note 10, at 694. For drugs that have been around for years, physicians do have access to the "Orange Book" published by the FDA. Physicians consult this book to sift through the approved uses and non-approved uses for drugs—thus they can distinguish between off and on-label usage marketing schemes. *See* Fed. Food & Drug Admin., *Orange Book*, FDA.GOV, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (last visited Apr. 27, 2015). However, this book does not always provide timely information for brand new drugs. *See id.*

143. Greene, *supra* note 10, at 694.

144. *Id.* at 702.

145. *Id.*

146. Outterson, *supra* note 100, at 15–16.

147. Greene, *supra* note 10, at 647.

as a non-issue by many drug and device manufacturers.[148] This is particularly concerning when considered in the context of antibiotic resistance, because two major driving forces behind this phenomenon are misuse and overuse.[149] Off-label promotion of antibiotics encourages physicians to use new antibiotics in ways or for conditions not independently approved by the FDA.[150] In fact, despite the general denial of the effect of marketers on their prescribing behavior, studies of physicians' knowledge of drug properties show that their knowledge is more in line with sales information than the medical literature.[151]

In short, pharmaceutical detailers use the trust physicians place in their statements to increase the number of prescriptions of a new drug. In the context of antibiotics, a large quantity of low quality prescriptions is disastrous and only perpetuates misuse.[152]

IV. CURRENT FEDERAL ACTION BEING TAKEN TO COMBAT ANTIBIOTIC RESISTANCE IS INCOMPLETE WITHOUT ADDRESSING OFF-LABEL PROMOTION OF NEW ANTIBIOTICS

A. Recent Legislation Aimed at Increasing Supply is Incomplete

Recently, the federal government has taken action to address the public health emergency posed by antibiotic resistance. In 2011, Congress first formally addressed the issue by passing the Generating Antibiotic Incentives Now (GAIN) Act.[153] The GAIN Act focuses

148. *Id.* at 648 ("Off-Label marketing has been described as 'so common among drug and device makers that it's often dismissed as the equivalent of driving slightly over the speed limit.'").

149. Sage & Hyman, *supra* note 21, at 791.

150. In 2005, the FDA reprimanded pharmaceutical company Pfizer for aggressively promoting a powerful new antibiotic call linezolid. The antibiotic was part of a new class and was being promoted by Pfizer as a treatment for all types of MSRA infections, even though the FDA had only approved linezolid for only limited MRSA indications. *See* Savert, *supra* note 6, at 433 n.11 (citing Letter from Thomas W. Abrams R.Ph., Officer, Pfizer, Inc. (July 20, 2005), *available at* http://www.fda.gov/cder/warn/2005/Zyvox_wl.pdf).

151. Kesselheim, *supra* note 11, at 248.

152. *See CDC Threat Report*, *supra* note 4.

153. Forsyth, *supra* note 96, at 3.

almost exclusively on incentivizing production of new antibiotics.[154] "The GAIN Act provides pharmaceutical companies [several] incentives to develop new antibiotics to combat the growing problem of antibiotic resistance."[155] For example, GAIN "[a]dds five years of exclusivity to qualified new antibiotics" and an "additional six months for antibiotics that are paired with a companion diagnostic test."[156] Additionally, GAIN provides priority and fast-track review of new antibiotics by the FDA.[157]

B. Regulating the Off-Label Promotion of New Antibiotics is a Practical Necessity

While legislation like GAIN is essential to address the lack of new antibiotic development, the Act is not a complete fix.[158] GAIN focuses on the supply/production side of the issue, with little to no focus on regulating the way these new antibiotics would be used or marketed.[159] Thus, the potential for off-label promotion of these new

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154. Forsyth, *supra* note 96, at 9.

155. *Id.*

156. *Id.*

157. *Id.* at 7; *see* 21 U.S.C. § 335(f) (2102) (exclusivity provision), 21 U.S.C. § 360(n) (2012) (fast-track and priority review provision). There are several distinctions between the Fast Track designation and the normal New Drug Approval (NDA process). "A drug that receives Fast Track designation is eligible for some or all of the following: (1) More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval; (2) more frequent written communication from FDA about such things as the design of the proposed clinical trials and use of biomarkers; (3) eligibility for *Accelerated Approval and Priority Review, if relevant criteria are met*; (4) *Rolling Review*, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA." Fed. Food & Drug Admin., *Fast Track*, FDA.GOV (last updated Sept. 15, 2014) http://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm.

158. *See* Forsyth, *supra* note 96, at 10–14.

159. Forsyth, *supra* note 96 at 9 ("[T]here are no provision encouraging appropriate use and marketing of new antibiotics to prevent antibiotic resistance to these new antibiotics.").

drugs for unapproved uses threatens to undermine any progress GAIN generates.

Incentivizing the production of new antibiotics and educating physicians and the general public about antibiotic resistance are essential to combating antibiotic resistance; however, this approach is incomplete without addressing how new antibiotics will be marketed.

As discussed *supra*, misuse and overuse of antibiotics are two primary factors that contribute to the rapid growth of antibiotic resistance.[160] Physicians' inaccurate or incomplete knowledge regarding an antibiotic or class of antibiotics often leads to misuse and overuse.[161] In most instances, the majority of the information about a new antibiotic comes from pharmaceutical marketing and sales representatives.[162] Unfortunately, these pharmaceutical companies face "an inherent conflict of interest between the legitimate business goals . . . and the social, medical and economic needs . . . to select and use [antibiotics] in the most rational way."[163] Thus, regulating how pharmaceutical sales representatives market to physicians may aid problems regarding inappropriate prescription of antibiotics. Off-label promotion is a common practice, especially during detailing sessions.[164] Empirical evidence shows that marketing practices influence physicians' prescription behavior and can increase the quantity—but not necessarily the quality—of that behavior.[165] Without preventing pharmaceutical makers, who have substantial financial incentives to increase the quantity of new antibiotics sold, from making unapproved and non-independently-verified claims about drug uses, any progress against the threat of antibiotic resistance may be lost.

The FDA may regulate pharmaceutical marketing under the misbranding provision of the FDCA.[166] But, recent judicial decisions

160. Sage & Hyman, *supra* note 21, at 791.

161. *CDC Threat Report*, *supra* note 4, at 11.

162. World Health Org., *Pharmaceutical Industry*, WHO.INT, http://www.who.int/trade/glossary/story073/en/ (last visited Jan. 2, 2015).

163. *Id.*

164. Greene, *supra* note 10, at 649.

165. *See* discussion *supra* Part III.

166. Greene, *supra* note 10, at 660; *see also* 21 U.S.C. §§ 321(k), (m) (2012); 21 C.F.R. § 202.1 (Deering 2014).

do not clearly state whether the FDA can constitutionally regulate off-label promotional statements that sales representatives make during detailing.[167] However, given the unique public health threat posed by antibiotic resistance, the FDA should have the ability to regulate off-label promotional statements made during the sale of new antibiotics. Such discretion will help ensure that aggressive and medically reckless marketing does not burden regulations that promote the development of new antibiotics.

V. HOW FDA RESTRICTIONS ON ANTIBIOTIC MARKETING CONTEND WITH COMMERCIAL FREE SPEECH

Courts should allow the FDA to regulate the off-label promotion of new antibiotics because of antibiotic resistance. The FDA appears to have the power to restrict off-label promotion of new antibiotics to promote public health. In fact, the FDA already regulates pharmaceutical marketing through its labeling provisions, including oral statements made by pharmaceutical representatives for promotional purposes.[168] However, pharmaceutical companies have objected to those types of regulations claiming the regulations violate their commercial free speech rights.[169] Recently some courts have agreed with that objection.[170]

In *Sorrell v. IMS Health Inc.*,[171] the United States Supreme Court recognized that pharmaceutical marketing is protected speech under the First Amendment.[172] Therefore, content-based, or speaker-based, regulations on such speech are subject to "heightened judicial scrutiny."[173] Relying on *Sorrell*, the Second Circuit Court of Appeals in *United States v. Caronia*,[174] held the FDCA misbranding provision

166. *See* discussion *infra* Part V.

167. *See* discussion *infra* Part V.

168. Greene, *supra* note 10, at 660; *see also* 21 U.S.C. §§ 321(k), (m) (2012); 21 C.F.R. § 202.1.

169. Greene, *supra* note 10, at 654.

170. *See generally* Greene, *supra* note 10.

171. Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011).

172. *Id.* at 2659.

173. *Id.*

174. United States v. Caronia, 703 F.3d 149 (2d Cir. 2013).

did not apply to off-label statements made by sales representatives during detailing sessions.[175] While the overall debate about the general restriction, or ban, of off-label promotion has not been settled, the FDA should have the power to restrict off-label promotion of new antibiotics. These restrictions would survive the *Sorrell* and *Caronia* strict scrutiny test.

A. Regulations Must Survive Strict Scrutiny Under Sorrell

FDA regulations on pharmaceutical marketing have recently come under strict constitutional scrutiny. Two recent cases highlight the constitutional hurdles that any FDA regulation regarding promotional statements may face.

First, in *Sorrell v. IMS Health Inc.*,[176] the Supreme Court analyzed a Vermont law that banned the sale of "physician prescribing information" to pharmaceutical companies for marketing purposes.[177] Prior to the law's enactment, pharmacies collected data on individual physicians based on what drugs physicians prescribed and how often the physicians prescribed specific drugs.[178] Pharmacies then sold that information to "data miners"[179] who processed the information into reports and leased those reports to pharmaceutical companies.[180] That process enabled the pharmaceutical companies to tailor their marketing strategies based on physicians' prescribing habits.[181] Opponents argued that the law unconstitutionally limited commercial speech of pharmaceutical sales representatives.[182]

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175. *Id.* at 165; *see also* Greene, *supra* note 10, at 645, 678.

176. *Sorrell*, 131 S. Ct. 2653.

177. *Sorrell*, 131 S. Ct at 2659. ("Physician prescribing information" is information about the prescription habits of individual physicians collected by pharmacies.").

178. *Id.*

179. "'[D]ata miners,' [are] firms that analyze prescriber-identifying information and produce reports on prescriber behavior." *Id.* at 2660.

180. *Id.*

181. *See id.* at 2660–61.

182. *Id.* at 2661.

The Court first recognized that pharmaceutical marketing is considered protected speech under the First Amendment.[183] Next, the Court concluded that banning the sale of that information to pharmaceutical companies for sales purposes was discriminatory.[184] The Court observed that pharmacies were allowed to sell, or share, physicians' prescription information to others, including research institutions or universities.[185] Therefore, the majority reasoned that the Vermont law disfavored "speech with a particular content [marketing] . . . [and] specific speakers" namely pharmaceutical manufacturers.[186] The Court further held that a law placing "content-based" or "speaker-based" restrictions on speech will be presumed invalid and subject to strict scrutiny.[187] In order to overcome that presumption, the State must show "that the [regulation] directly advances a substantial governmental interest and that the measure is drawn to achieve that interest."[188]

Second, in *United States v. Caronia*, the majority of the Second Circuit Court of Appeals used the analysis from *Sorrell* to conclude that the FDCA's provisions against misbranding could not be applied to sales representatives' off-label promotional statements.[189] There, the federal government investigated a pharmaceutical sales representative for violating the FDCA's provisions against misbranding.[190] During trial, the Government cited off-label promotional statements—directly contradicting the FDA's black box label for the product[191]—made by the defendant during his detailing trips to physicians' offices.[192] The Government argued that these

183. *Id.* at 2659.

184. *Id.* at 2656–57.

185. *Id.* at 2661, 2663 ("[P]harmacies may sell the information to private of academic researchers but not, for example, to pharmaceutical marketers.").

186. *Id.* at 2656–57.

187. *Id.* at 2667.

188. *Id.*

189. *See generally* United States v. Caronia, 703 F.3d 149, 166–69 (2d Cir. 2013); *see also* Greene, *supra* note 10, at 674–80.

190. *Caronia*, 703 F.3d at 160–61.

191. *Id.* at 156–57.

192. *Id.* at 160–61 (The court did not address the accuracy of the promotional information and assumed it to be truthful. Caronia asserted the information was

statements, made during detailing sessions, were evidence of the defendant's intent to introduce a drug into the stream of commerce for an unapproved use violating the FDCA's misbranding provisions.[193] In response, the defendant argued that the provisions violated his First Amendment rights under *Sorrell*, because they imposed both "speaker-based" and "content-based" restrictions on protected speech.[194]

Relying on *Sorrell*, the majority agreed that the defendant's speech was protected.[195] *Caronia* held the FDCA's misbranding provisions, as-applied, failed to satisfy the test mandated by *Sorrell* because the provisions: (1) did not advance a substantial government interest; and (2) were not narrowly drawn.[196] The court reasoned that the provisions did not directly advance a government interest, because off-label prescription is lawful, and physicians can acquire information about off-label uses from sources other than sales representatives.[197] Additionally, the court suggested the FDCA's misbranding provisions, as applied to off-label promotion, were not narrowly drawn, because other methods were available that could achieve the same governmental interests.[198]

Any FDA regulation seeking to restrict promotional speech must, therefore, survive the strict scrutiny of *Sorrell*. The following subsections address each element of the First Amendment analysis as applied to FDA regulations of the off-label promotion of new antibiotics, and distinguish this type of off-label promotion from that discussed in *Caronia*.

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truthful and the FDA did not challenge this assertion. Therefore, the court did not deal with the accuracy of the claims.).

193. *Id.* at 160.

194. *Id.* at 164, 166.

195. *Id.* at 162.

196. *Id.*

197. *Id.*

198. *See id.* at 168 (Although the court lists several alternative options, the court did not address the validity of these potential "other methods.").

1. Responding to Antibiotic Resistance is a Substantial Government Interest

Allowing the FDA to regulate the off-label promotion of new antibiotics promotes a substantial government interest. Courts recognize that the government has a substantial interest in protecting the health and safety of American citizens.[199] Antibiotic resistance threatens both the health and safety of American citizens on a global scale.[200]

Additionally, courts have recognized that the government has a separate, but closely related, substantial interest in preserving the integrity and effectiveness of the FDA's premarket drug-approval processes.[201] Prior to 1962, the FDCA did not require drugs to be tested for effectiveness before being marketed.[202] However, after a decade of congressional hearings on the matter, Congress recognized that this system endangered the health of American citizens.[203] The hearings revealed that physicians relied on misleading promotional material and with "no reliable source of evidence from which physicians could tell effective drugs from ineffective drugs," many Americans "were being subjected unnecessarily to toxic drugs whose benefits had been greatly exaggerated or were nonexistent."[204] Thus, in 1962 congress passed the 1962 Drug Amendments to the FDCA. The Amendments emphasized the importance of premarket review by an objective body.[205] Off-label promotion undermines this process by promoting drugs that have not been independently reviewed by the FDA.[206]

Still further, courts have recognized that the "purpose of the commercial speech doctrine is to protect consumers from misleading,

199. Greene, *supra* note 10, at 675.
200. *See* discussion *supra* Part I.
201. *See* Greene, *supra* note 11, at 681–82; Waxman, *supra* note 113, at 309.
202. Waxman, *supra* note 113, at 300–01.
203. *See generally* Waxman, *supra* note 113.
204. *Id.* at 301–02.
205. *Id.* at 307.
206. Greene, *supra* note 10, at 658.

deceptive or aggressive sales practices."[207] Congress passed the FDCA because it recognized that pharmaceutical companies and their representatives "face perverse financial incentives that encourage the inappropriate use of [antibiotics] . . . ."[208] This is particularly relevant in the context of new antibiotics and antibiotic resistance. The fact that pharmaceutical companies profit from increasing the number of antibiotics prescriptions, encourages aggressive marketing.[209] This is particularly true at the beginning of a new antibiotic's market life when the patent period is still valid.[210] Therefore, courts have recognized a substantial government interest in subjecting new drugs to the FDA's pre-market approval process.[211] Accordingly, restricting the off-label promotion of new antibiotics promotes the government's substantial interest in practically addressing antibiotic resistance.

2. *Restricting Off-Label Promotion of Antibiotics for Use in Medicine Directly Advances the Government's Interest*

Finally, recent federal action is evidence that controlling the spread of antibiotic resistance is a substantial government interest.[212] In addition to the GAIN Act, in September of 2014, President Obama enacted an Executive Order providing a federally coordinated approach to combat antibiotic resistance.[213] The Order called for the FDA and pharmaceutical companies to collaborate in disseminating information to physicians regarding appropriate new uses of antibiotics.[214] Allowing the FDA to regulate off-label promotion of

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207. *Id.* at 646 (quoting Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 64–65 (D.C. Cir. 1998)).

208. Outterson, *supra* note 100, at 17. This inappropriate use includes misuse and overuse.

209. *Id.*

210. *Id.*

211. Waxman, *supra* note 113, at 309.

212. *See* discussion *supra* Part III.

213. *See* Exec. Order No. 13,676, 79 Fed. Reg. 56931 (Sept. 18, 2014), https://federalregister.gov/a/2014-22805; *see also National Strategy for Combating Antibiotic-Resistant Bacteria*, WHITEHOSE.GOV (published Sept. 2014), *available at* http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf.

214. *See* Exec. Order No. 13,676, 79 Fed. Reg. 56931 (Sept. 18, 2014), https://federalregister.gov/a/2014-22805.

new antibiotics directly advances the government's interest in slowing antibiotic resistance. Because off-label marketing of new antibiotics can have a substantial and direct effect on physician prescription behaviors and could lead to the misuse and overuse of new antibiotics the FDA should have the power to regulate such off-label promotion.[215]

Allowing off-label promotion of new antibiotics not only poses a risk to public health, but directly undermines the foundation of the FDA's drug-regulation system.[216] Physicians rely on promotional information to prescribe new drugs, including antibiotics.[217] Off-label promotional information, particularly in the use of detailing, has been linked to an increase in prescription quantity, but not necessarily quality, thus perpetuating misuse and overuse.[218] Pharmaceutical companies may argue that banning off-label promotion would not directly advance the government's interest, because physicians are able to evaluate the information provided by marketers and do not primarily rely on this information when making medical decisions.[219] However, although physicians generally agree with that contention, studies confirm that physicians are heavily influenced by marketing, and their knowledge about any given drug is incomplete.[220] Despite this, as the Supreme Court noted in *Sorrell*, fear that speech is too persuasive is not grounds for its regulation.[221] The Court stated that Vermont failed to show a clear indication that the detailer's use of prescriber identifiable information jeopardized the integrity of the physician-patient relationship.[222] Thus, the fact that the

215. *See* discussion *supra* Part III.

216. Greene, *supra* note 10, at 682 ("[I]f drug manufacturers have a First Amendment right to distribute drugs for any use to physicians or even directly to patients, then the entire FDCA may well be unconstitutional.") (internal quotations omitted).

217. *See* Vukadin, *supra* note 129, at 81.

218. *See id.* at 83.

219. Waxman, *supra* note 113; Kesslheim, *supra* note 11, at 248–49 (outlining the role of pharmaceutical marketing in physician decision-making and the response of pharmaceutical companies).

220. *See* Waxman, *supra* note 113; Kesslheim, *supra* note 11, at 248–49.

221. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2671 (2011).

222. *Id.*

pharmaceutical representatives were persuasive during their sessions with physicians was insufficient to justify restricting speech.[223]

In contrast to the law in *Sorrell*, off-label promotion of new antibiotics *does* directly jeopardize the physician-patient relationship. Additionally, off-label promotion perpetuates the public health crisis of antibiotic resistance because it encourages misuse and overuse. When a new antibiotic enters the market, physicians have limited information, the only information on intended uses and effects of the antibiotics is that printed on the FDA label and contained in the promotional material pharmaceutical sales representatives provide.[224] Physicians cannot rely on the FDA's review for off-label uses, and there is no guarantee that an objective review of those uses even occurred.[225] Off-label promotion is an issue because there could "easily [be] selective presentation of data [by detailers] intended to support the [unapproved] use of the product."[226]

Additionally, off-label promotion is problematic in that it decreases incentives for pharmaceutical companies to seek additional FDA approval for off-label uses.[227] The court in *Caronia* expressly recognized that pharmaceutical companies have little incentive to seek additional approval for off-label uses because the approval process is expensive.[228] Therefore, restricting marketing behavior is only one method for the FDA to encourage companies to seek additional approval for additional uses of a new antibiotic.[229]

Regulating the off-label promotion of new antibiotics directly advances the government's substantial interest of combating the spread of antibiotic resistance by reducing misuse and overuse. Restricting the off-label promotion of new antibiotics also encourages pharmaceutical companies to seek proper FDA approval for additional uses, maintaining the integrity of the drug-regulatory system.

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223. *Id.* (explaining that the law at issue banned the sale of prescriber identifying information to pharmaceutical companies for marketing purposes).

224. *See* Kesselheim, *supra* note 11, at 248.

225. *See id.* at 251.

226. *Id.* at 250.

227. *See* Greene, *supra* note 10, at 676.

228. *Id.*

229. *Id.*

3. Specific Restrictions on the Off-Label Promotion of Antibiotics is Practically Drawn to Achieve the Interest of Protecting Public Safety by Addressing Antibiotic Resistance

Allowing the FDA to regulate the off-label promotion of antibiotics can be narrowly drawn to address the specific concern of antibiotic resistance. In many cases, courts often deal with general off-label promotion by finding this element, being narrowly drawn, to be unsatisfied.[230] However, a suggestion for restricting off-label promotion of new antibiotics is not a suggestion for a blanket ban on off-label promotion. These regulations would apply only to the off-label promotion of new antibiotics.

The regulations proposed here would specifically: (1) allow the FDA to ban the printing of off-label uses for new antibiotics, unless that use is currently being approved by the FDA and is accompanied by a disclaimer; and (2) allow the FDA to ban pharmaceutical sales representatives from making statements promoting an off-label use of a new antibiotic. Regulating off-label promotion specifically for new antibiotics is an important distinction, because off-label promotion poses specific problems when applied to new antibiotics and antibiotic resistance. When an antibiotic is promoted—and later prescribed—for an ineffective off-label use, it may add unnecessary selection pressures that create antibiotic resistance.[231] Even without endangering an individual patient's safety, an improperly prescribed antibiotic is dangerous to the population at large because of its impact on the development of antibiotic resistance.[232] In other words, in the context of antibiotics, it is not the mere threat of danger that this regulation addresses, but an actual present danger.

The Supreme Court recognizes disclaimers and disclosures as alternatives to prohibitions on commercial speech."[233] Therefore, courts often suggest disclaimers as viable alternatives to regulating off-label promotion.[234] However, as Judge Livingston suggested in

230. *See generally id.*
231. *See supra* Part I.A.
232. *See supra* Part I.A.
233. Kesselheim, *supra* note 11, at 246.
234. *See* Greene, *supra* note 10, at 683.

the dissenting opinion in *Caronia*, disclaimers are often ineffective and can potentially encourage pharmaceutical companies to bypass the approval process.[235] To overcome this hurdle, the proposed regulation of off-label promotion would allow for companies seeking FDA approval for additional uses to print this information in their promotional material as long as it is accompanied by a disclaimer. Allowing oral disclosure is impractical because it is impossible to enforce. A physician listening to a sales pitch is not listening for an off-label use and may not know when a disclaimer should have been made. Furthermore, oral disclosure would be extremely difficult to enforce since most detailing conversations are not recorded, and it is difficult for physicians to remember whether a disclaimer was given. Thus, pharmaceutical companies would not be able to promote off-label uses of new antibiotics through oral or written statements; however, if a company is seeking FDA approval for an additional use, that information would be allowed to be printed with a disclaimer but would not be permitted to be the centerpiece of the promotional material. This regulation is not overly broad, because it focuses on only two types of off-label promotion, only applies to antibiotics, allows for disclaimers, and is intended to address the serious root causes of antibiotic resistance—misuse and overuse of new drugs.

CONCLUSION

Fatal bacterial infections are not as ghost-like as they may appear. Antibiotic resistance is resurrecting these ghosts—and fast. Without real and practical solutions that address antibiotic resistance, the problems of our past are poised to become the bane of our future. Even if current legislation like the GAIN Act achieves its goals and promotes the production of new antibiotics, without proper control of off-label promotion, new antibiotics could become just as ineffective as the ones they replace.

Admittedly, the government cannot directly control how physicians practice medicine. However, the FDA can control how pharmaceutical companies promote new antibiotics to physicians. Because marketing influences how and when physicians prescribe

235. *Id.*

drugs, it is essential that the FDA be able to hold pharmaceutical companies responsible for ensuring that physicians receive accurate and objectively verifiable information about new antibiotics.

While protecting speech is essential, the nation is currently at risk of losing effective antibodies to combat infections. The FDA, should have the power to regulate the content of speech regarding the promotion of new antibiotics to preserve the efficacy of modern medicine.

*Erin LaMontagne**

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* Doctor of Jurisprudence Candidate at California Western School of Law, and expects to receive her J.D. in May 2016. The author would like to thank Professor Robert Bohrer and her colleagues on the California Western Law Review for all of their help and support.