

IMPROVING ANTIBIOTIC MARKETS FOR LONG TERM SUSTAINABILITY

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INTRODUCTION	2
I. ANTIBIOTIC RESISTANCE.....	12
II. THE LIMITATIONS OF NEW ANTIBIOTIC DEVELOPMENT.....	15
III. EXISTING PARADIGMS TO PROMOTE CONTINUED ANTIBIOTIC EFFECTIVENESS	22
A. ANTIBIOTIC CONSERVATION	23
B. PROPERTY-BASED INCENTIVES	28
1. PATENT EXTENSIONS	30
2. TRANSFERABLE INTELLECTUAL PROPERTY RIGHTS.....	33
C. REIMBURSEMENT INCENTIVES BASED ON MEDICAL NEED	35
D. REDUCING FINANCIAL HURDLES FOR ANTIBIOTIC INNOVATION	38
1. ENHANCED BASIC SCIENCE FUNDING	39
2. ANTIBIOTICS UNDER THE ORPHAN DRUG ACT	40

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3. REDUCING THE COSTS OF REGULATION	44
E. CONCLUSION	48
IV. THE ANTIBIOTIC CONSERVATION AND EFFECTIVENESS (ACE) PROGRAM	50
A. VALUE-BASED REIMBURSEMENT OF ANTIBIOTICS	51
B. CONDITIONING REIMBURSEMENT ON MEETING CONSERVATION TARGETS	54
D. LIMITED WAIVERS OF ANTITRUST AND SELF-DEALING LAWS	58
V. IMPLEMENTATION ISSUES WITH ACE INCENTIVES	60
A. DESIGNING VALUE-BASED REIMBURSEMENT	60
B. THE STRATEGIC ANTIBIOTIC RESERVE	62
C. OTHER CONSIDERATIONS	63
1. INTELLECTUAL PROPERTY	63
2. ACCESS TO GENERIC ANTIBIOTICS	65
3. PUBLIC INVESTMENT IN ANTIBIOTIC RESEARCH	65
4. CROSS-BOUNDARY ANTIBIOTIC MANAGEMENT ISSUES	66
CONCLUSION	68

INTRODUCTION

The widespread introduction of antibiotics was one of the greatest medical accomplishments of the twentieth century, but our success in treating infectious diseases has led to a new public health challenge—the emergence and proliferation of microorganisms resistant to standard antibacterial therapy.¹ Unfortunately, legal and market structures in the United States have created a substantial gap between the private and social value of antibiotics, leading to problematic supply and demand incentives and increasingly resistant infections. Both hospitals² and community settings³ report growing resistance problems.

1. We use the term “antibacterial” or “antibiotic” throughout, with full recognition that many of the concepts discussed herein also apply to the broader category of antimicrobial agents. We focus on the narrower category because antivirals and antiretrovirals may present novel resistance and incentive issues that require separate treatment. For example, as discussed below, entry of low-cost, generic antiretrovirals has saved millions of lives in the battle against AIDS, but similar outcomes from generic entry have not been reported in the antibiotic market.

2. See John P. Burke, *Infection Control—A Problem for Patient Safety*, 348 NEW ENG. J. MED. 651 (2003); L. Silvia Munoz-Price & Robert A. Weinstein, *Acinetobacter Infection*, 358 NEW ENG.

Multidrug resistant bacteria are a grave public health concern because they put patients at risk for serious illness and possibly death,⁴ and they place increased demand on already strained health care resources.⁵ Patients with resistant infections can lead to increased inpatient hospital costs,⁶ outpatient treatment costs,⁷ and long-term care spending.⁸ Life in a post-antibiotic era would be remarkably different and less healthy.

Leading academic groups, public health organizations, and governments have recently become more vocal about the problem of drug-resistant infections. The Infectious Diseases Society of America (IDSA) reported that “[i]nfections that were once easily curable with antibiotics are becoming difficult, even impossible, to treat, and an increasing number of people are suffering severe illness—or dying—as a result.”⁹ The Alliance for the Prudent Use of Antibiotics has been focused for many years on resistance stemming from the misuse of antibiotics.¹⁰ Government agencies in the United States¹¹ and other countries have given increasing attention to the topic; as the Select Committee on Science and Technology in the United Kingdom House of Lords noted:

“[T]he inevitable rise and spread of resistance will render existing drugs progressively less useful. In the absence of new drugs, this leaves us increasingly at the mercy of infections. We cannot eliminate resistance. We can

J. MED. 1271 (2008); Melinda M. Neuhauser et al., *Antibiotic Resistance Among Gram-Negative Bacilli in US Intensive Care Units: Implications for Fluoroquinolone Use*, 289 JAMA 885 (2003).

3. See J. Patrick Powell & Richard P. Wenzel, *Antibiotic Options for Treating Community-Acquired MRSA*, 6 EXPERT REV. ANTI-INFECTIVE THERAPY, 299 (2008).

4. See Yehuda Carmeli et al., *Health and Economic Outcomes of Vancomycin-Resistant Enterococci*, 162 ARCH. INT. MED. 2223 (2002).

5. Rebecca H. Sunenshine et al., *Multidrug-Resistant Acinetobacter Infection Mortality Rate and Length of Hospitalization*, 13 EMERGING INFECTIOUS DISEASES 97 (2007).

6. Heather L. Evans et al., *Cost of Gram-Negative Resistance*, 35 CRIT. CARE MED. 89 (2007).

7. See Carl Asche et al., *Treatment Costs Associated with Community-Acquired Pneumonia by Community Level of Antimicrobial Resistance*, 61 J. ANTIMICROBIAL CHEMOTHERAPY 1162 (2008).

8. See Blair Capitano et al., *Cost Effect of Managing Methicillin-Resistant Staphylococcus Aureus in a Long-Term Care Facility*, 51 J. AM. GERIATRIC SOC’Y 15-16 (2003).

9. INFECTIOUS DISEASES SOC’Y OF AM., BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES . . . A PUBLIC HEALTH CRISIS BREWS 9 (2004), available at <http://www.idsociety.org/10x20.htm> [hereinafter BAD BUGS].

10. Stuart B. Levy, *Antibiotic and Antiseptic Resistance: Impact on Public Health*, 19 PEDIATRIC INFECTIOUS DISEASE J. S122 (2000).

11. See generally FDA TASK FORCE ON ANTIMICROBIAL RESISTANCE: KEY RECOMMENDATIONS AND REPORT (2000), available at <http://www.fda.gov/oc/downloads/ForConsumers/ConsumerUpdates/UCM243458.pdf>

however slow it down, by using antibiotics only when necessary, and by rigorous infection control and basic hygiene, both informed by thorough surveillance.”¹²

Many groups, including the Center for Global Development,¹³ the London School of Economics,¹⁴ Resources for the Future,¹⁵ and the Swedish Presidency of the European Union,¹⁶ have recently published reports on global antibiotic resistance. Despite this focused attention, few concrete, affirmative steps have been taken, and the threat of resistance grows.

We believe that one of the primary contributors to the problem of antibacterial resistance lies in the market for antibiotics, and specifically how markets reimburse for drug development and use in this field. Current legal structures and market incentives unwittingly accelerate resistance in several ways, all rooted in the mismatch between private and social value. First, Medicare and U.S. private payor reimbursement¹⁷ create certain market incentives without adequate concern for the potential social impact on resistance. For example, for many years, federal reimbursement under Medicare has rewarded hospital-associated infections with additional payments, while failing to reimburse for conservation and infection control. While hospitals have significant non-financial reasons to control hospital-acquired infections, this policy paradoxically rewards bad behavior by paying for hospital infections.¹⁸ Or

12. SCI. AND TECH. SELECT COMM. OF THE HOUSE OF LORDS, THIRD REPORT: RESISTANCE TO ANTIBIOTICS para. 3 (2001), *available at* <http://www.publications.parliament.uk/pa/ld200001/ldselect/ldsctech/56/5602.htm>.

13. RACHEL NUGENT, EMMA BACK & ALEXANDRA BEITH, CTR. FOR GLOBAL DEV., THE RACE AGAINST DRUG RESISTANCE (2010), *available at* <http://www.cgdev.org/content/publications/detail/1424207>. Professor Outtersen was a member of the Working Group on Drug Resistance at the Center for Global Development.

14. ELIAS MOSSIALOS ET AL., LONDON SCH. OF ECON., POLICIES AND INCENTIVES FOR PROMOTING INNOVATION IN ANTIBIOTIC RESEARCH (2010), *available at* http://www.se2009.eu/polopoly_fs/1.16814!menu/standard/file/LSE-ABI%20F-Final.pdf. This monograph was funded by a grant from the Swedish government.

15. RAMANAN LAXMINARAYAN ET AL., EXTENDING THE CURE: POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE (2007), *available at* <http://www.extendingthecure.org/report>.

16. SWEDISH PRESIDENCY OF THE EUROPEAN UNION, INNOVATIVE INCENTIVES FOR EFFECTIVE ANTIBACTERIALS (2009), *available at* http://www.se2009.eu/polopoly_fs/1.25861!menu/standard/file/Antibacterials5.pdf.

17. While our analysis has broader implications, we draw many of our market examples from the United States.

18. Kevin Outtersen, Germ Shed Management (2010) (unpublished manuscript, on file with

take the example of infection control, which experts have lauded as an effective public health measure that also conserves antibiotics. Medicare does not have a billing code for infection control practices. Because it is not reimbursed, infection control does not directly generate revenue.

Second, some well-intentioned efforts work at cross-purposes, undermining effectiveness at a population health level. For instance, 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.¹⁹ This is a classic example of social value exceeding private value.²⁰ Another example of antagonistic incentives involves antibiotic conservation and infection control programs. These initiatives reduce the inappropriate demand for antibiotics, prevent unnecessary infections, and therefore preserve the drugs for more valuable uses. Society benefits, but drug companies point out that these programs undercut antibiotic sales.²¹ Citing the lack of appropriately sized and predictable markets, some drug companies have fled from antibiotic research, despite the significant clinician demands for additional effective therapies. The interactive and dynamic effects among these policy options must be mapped and addressed.

Finally, we must evaluate the cost-effectiveness of potential interventions on a population level. From society's perspective, the NIH severely underfunds

author).

19. The "patent holder waste" hypothesis posits that the patent holder of an antimicrobial will tend to over-market (and thereby waste) the product as patent expiry approaches, delivering an exhausted antimicrobial to the public domain when generic entry looms. See Eric Kades, *Preserving a Precious Resource: Rationalizing the Use of Antibiotics*, 99 NW. U. L. REV. 611, 648-52 (2005). But see Kevin Outterson, *The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation*, 31 CARDOZO L. REV. 613 (2010) [hereinafter *Legal Ecology of Resistance*] (developing the theory of patent holder waste); Kevin Outterson, *The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Intellectual Property Law*, 67 U. PITT. L. REV. 67, 78-80 (2005) [hereinafter *Vanishing Public Domain*] (critiquing Kades' approach).

20. Some policy experts claim that the social value of pharmaceuticals generally exceeds their private value. See, e.g., J.D. Kleinke, *The Price of Progress: Prescription Drugs in the Health Care Market*, 20 HEALTH AFF. 43 (2001). For a contrary example of the private value of information exceeding the social value, see Jack Hirshleifer, *The Private and Social Value of Information and the Reward to Inventive Activity*, 61 AM. ECON. REV. 561, 565-66 (1971).

21. See Steven J. Projan, *Why is Big Pharma Getting Out Of Antibacterial Drug Discovery?*, 6 CURRENT OPINION MICROBIOLOGY 427, 428-30 (2003).

basic research into antibacterial resistance.²² Private markets are unlikely to pick up the slack in basic antibiotic research because private actors undersupply products with common pool or public goods characteristics. On the other hand, some research programs, such as additional antibiotics for self-resolving minor infections, appear to be privately valuable, but unnecessary at a population level. Some recent proposals could generate private financial gains for companies, though they might be counterproductive or cost-ineffective at the population level. One example is the proposal to grant wild-card patents for antibiotics, rewarding drug companies for antibiotic innovation by granting a longer patent on any other drug in the company's portfolio.²³ Wildcard patent proposals may cost many billions of dollars, with doubtful social value.²⁴ Essentially, wildcard patents tax drugs for heart disease to pay for antibiotic research and development. We should not pursue such options without adequately modeling the potential gaps between private and social cost, as well as the opportunity cost.

In previous work, we have described some of the policy options available to promote continued antibiotic effectiveness.²⁵ Table 1 displays these options graphically, dividing the policy options into eight Sectors. The columns in Table 1 are the two intermediate policy goals: conservation of existing antibiotics and the production of new ones. While we have conceptually separated conservation and production into columns, the ultimate policy goal remains continued antibiotic effectiveness. Policymakers will need to balance both conservation and production to achieve that goal over time. The rows represent the four primary legal tools that can be deployed to achieve these goals: property, regulation, contract, and tort.²⁶ With Table 1, one can see a broad array of policy options, eight Sectors in all.

22. N. Kent Peters et al., *The Research Agenda of the National Institute of Allergy and Infectious Diseases for Antimicrobial Resistance*, 197 J. INFECTIOUS DISEASE 1087, 1087 (2008).

23. See *infra* Section III.B for a critique of patent-based incentives for antibiotic development.

24. Kevin Outterson, Julie Balch Samora & Karen Keller-Cuda, *Will Longer Antimicrobial Patents Improve Global Public Health?*, 7 LANCET INFECTIOUS DISEASES 559, 559 (2007) [hereinafter *Longer Antimicrobial Patents*].

25. Aaron S. Kesselheim & Kevin Outterson, *Fighting Antibiotic Resistance: Marrying New Financial Incentives to Meeting Public Health Goals*, 29 HEALTH AFF. 1689, 1692-94 (2010) [hereinafter, *Fighting Antibiotic Resistance*]; Outterson, *supra* note 19, at tbl.1 (outlining six possible policy sectors for addressing continued antibiotic effectiveness, using property, regulation and contract to improve antibiotic conservation and production).

26. For examples of legal and health policy scholarship in Sectors 1-6, see Outterson, *supra* note 19, at 621-26.

TABLE 1: CONCEPTUAL LEGAL APPROACHES TO CONTINUED ANTIBIOTIC EFFECTIVENESS

	Conservation	Production
Property	Patents used as conservation tools to privately constrain demand. (Sector 1)	Patents used as incentives to bring new antibiotics to market. (Sector 2)
Regulation	Public health infection control and antibiotic stewardship programs regulate demand for antibiotics. (Sector 3)	FDA regulations relaxed to speed approval of new antibiotics. Tax subsidies support R&D. (Sector 4)
Contract	Prizes, grants, and value-based reimbursement support antibiotic conservation. (Sector 5)	Prizes, grants, and value-based reimbursement support new antibiotic production. (Sector 6)
Tort	Patients sue for hospital-associated infections, increasing institutional incentives to promote safety through antibiotic conservation. (Sector 7)	Federal law designed to preempt state tort law, waiving drug company tort liability for antibiotics, similar to the national vaccine injury compensation program. (Sector 8)

This Article builds on our previous work by describing in-depth a range of integrated policy solutions that address the problem of antibiotic resistance. Our guiding premise is that society's primary goal should be continued antibiotic effectiveness on a population level by giving proper incentives to various institutions and actors. We emphasize a balanced approach between production of new products and conservation of existing drugs, mirroring a similar shift that is currently underway in energy policy.

Our approach departs from the conventional wisdom in several ways. Most dramatically, we focus economic incentives for conservation on the drug companies themselves, since we believe they are best positioned to act on superior information, if only their economic incentives were realigned. While supporting conservation incentives for providers and others, our primary contribution to the literature is to ensure that drug companies fully embrace antibiotic conservation. Secondly, we focus our efforts on Sectors 5 and 6 – voluntary contracts whereby governments reward patent owners for managing their resources for long-term public health. Our approach is novel in the legal literature. Legal scholarship on drug development has traditionally focused on

property-based tools, especially the production of new drugs through patents (Sector 2).²⁷ With the notable exceptions of work by Eric Kades²⁸ and the “Extending the Cure” project by Ramanan Laxminarayan and Anup Malani,²⁹ legal scholarship has generally overlooked property-based conservation incentives designed to prolong antibiotic effectiveness for existing drugs, as well as other contract-based production incentives.³⁰ Some authors have descriptively catalogued the application of tort law to infections, but without a larger theoretical framework that includes production incentives.³¹ Other legal scholars have described regulatory tools in Sectors 3 and 4, as well as cultural and professional influences on antibiotic prescribing practices.³² A recent article by William Sage and David Hyman takes a broader approach, cataloguing many possible regulatory strategies.³³ The medical literature has often focused on Sector 3 conservation programs in isolation, without adequate analysis of the dynamic effects of multiple interventions and the legal and reimbursement environments. In the United States, most conservation and infection control studies focus on single hospitals, missing the positive externalities generated

27. See Outterson, *supra* note 19, at 620.

28. See Eric Kades, *supra* note 19, at 643-53 (2005).

29. LAXMINARAYAN ET AL., *supra* note 15.

30. Outterson, *supra* note 19, at 622. In recent years, several scholars have discussed the potential for value-based reimbursement or pay-for-performance as an antidote for hospital-associated infections. See, e.g., Rachel Deutsch, *The Federal Role in Reducing Hospital-Acquired Conditions: Are Medicare Reimbursement Incentives Enough?*, 42 COLUM. J.L. & SOC. PROBS. 1 (2008); David A. Hyman & Charles Silver, *You Get What You Pay For: Result-Based Compensation for Health Care*, 58 WASH. & LEE L. REV. 1427 (2001) (briefly discussing nosocomial infections).

31. Several authors have described tort-based approaches that would fit in Sector 7 (see Table 1). See, e.g., Jennifer M. Miller, *Liability Relating To Contracting Infectious Diseases in Hospitals*, 25 J. LEGAL MED. 211 (2004) (finding few effective tort remedies against hospitals and suggesting tort liability against health insurers as the better approach); Pamela Nolan, *Unclean Hands: Holding Hospitals Responsible for Hospital-Acquired Infections*, 34 COLUM. J.L. & SOC. PROBS. 133 (2000); William M. Sage & David A. Hyman, *Combating Antimicrobial Resistance: Regulatory Strategies and Institutional Capacity*, 84 TUL. L. REV. 781 (2010); Robert Steinbach, *Dirty Business: Legal Prophylaxis for Nosocomial Infections*, 97 KY. L.J. 505 (2008) (describing the positive role tort law can have to promote hospital safety against acquired infections) and. For an example of a related Sector 8 approach, see Lincoln Mayer, *Immunity for Immunizations: Tort Liability, Biodefense, and Bioshield II*, 59 STAN. L. REV. 1753 (2007).

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

33. See Sage and Hyman, *supra* note 31, for a discussion on the regulatory institutions relating to antibiotic resistance. [OP: This needs a pincite.]

when multiple institutions cooperate across a region.³⁴ Recent proposals to weaken antibiotic clinical trial requirements are Sector 4 initiatives.³⁵ In short, legal and medical scholarship has not adequately focused on antibiotic issues in the remaining Sectors, especially contract law (5 and 6)³⁶ and the complex interactions between conservation and production.

To remedy this gap in the literature, we offer an overview of medical, legal, and market forces that affect antibiotic production and conservation. Furthermore, we present a novel cluster of integrated solutions, centered in contract law,³⁷ which we call the Antibiotic Conservation and Effectiveness (ACE) program. The ACE program emphasizes: (1) value-based reimbursement of antibiotics from public payors such as Medicare and Medicaid, with spillover participation from private payors, in order to improve private markets for antibiotic effectiveness by providing financial incentives to promote continued antibiotic effectiveness; (2) making these payments conditional on meeting realistic public health and conservation goals, including a Strategic Antibiotic Reserve; (3) market-enhancing regulatory changes, including limited waivers of antitrust and other laws, to permit market coordination for conservation (supporting efforts in multiple Sectors); and (4) increased public grant support for basic antibiotic research, including both conservation and new production.

The first element of the ACE program is value-based reimbursement for antibiotics, increasing the private value of these drugs to more closely resemble the social value. Changes in reimbursement can have a remarkable impact on how antibiotics are created and used. For too long, antibiotics have been seen as cheap drugs, when in fact they are valuable exhaustible goods.³⁸ Improved

34. See Outterson, *supra* note 18.

35. BAD BUGS, *supra* note 9; Cecilia H. Burke & Geoffrey M. Levitt, *A Manufacturer's Perspective: Recent Challenges in Antibiotic Drug Approval*, 2 UPDATE: FOOD & DRUG L. REG. & ED. 12 (2008); Steven J. Projan & David M. Shlaes, *Antibacterial Drug Discovery: Is It All Downhill From Here?*, 4 CLINICAL MICROBIOLOGY & INFECTION. 18 (2004).

36. *But see* Sage & Hyman, *supra* note 33, at 799-803 (discussing improvements to information and public reporting of nosocomial infections). Tort law (Sectors 7 and 8) are discussed in a draft manuscript. See Outterson, *supra* note 18.

37. We treat health insurance reimbursement as a form of contract law, even though the market includes some elements of monopolies and monopsonies, as well as significant government regulation. Similarly, we treat grants as contracts, voluntarily entered into by the parties. Issues of tort law will be saved for another day.

38. Recently, antibiotics have been featured prominently in low-cost generic drug dispensation programs by many national retail pharmacies. For example, Wal-Mart's low-cost program allows patients to buy twelve different varieties of the antibiotic amoxicillin for \$4 per month. See Wal-Mart \$4 Medication List, [http://www.usatoday.com/money/industries/health/drugs/walmart-](http://www.usatoday.com/money/industries/health/drugs/walmart-9)

systems of reimbursement can support usage patterns more in tune with the intrinsic value of these drugs, as well as support the rational development of new ones. Our proposal includes prizes to promote antibiotic innovation as a form of reimbursement. James Love has posited prizes and reimbursement as conflicting choices for antibiotic innovation,³⁹ but we tend to see them as complementary, so long as prices at the point of care do not increase. In our proposal, the price paid by patients is not directly affected by value-based reimbursement. We focus on how the patent holders are reimbursed by private and public health plans. One mechanism might be a voluntary contract between the federal government and the patent holder, promising a significant financial prize in line with the public health impact of the drug, akin to James Love and Tim Hubbard's extensive proposals for drug R&D prizes⁴⁰ or Thomas Pogge and Aidan Hollis' Health Impact Fund.⁴¹

The second element of the ACE program makes these payments conditional:

druglist.pdf (last visited Dec. 3, 2010). While such generic drug programs have been rightly extolled for helping promote access and adherence to essential medicines, low-cost antibiotic access has been linked to overuse of these drug, particularly in lower-income settings. Beatriz Espinosa Franco et al., *The Determinants of the Antibiotic Resistance Process*, 2 INFECTION DRUG RESISTANCE 1 (2009); see also Karen Caffarini, *Antibiotic Giveaways Stoke Fear of Patient Pressure*, AM. MED. NEWS, Jan. 29, 2009, <http://www.ama-assn.org/amednews/2009/01/26/bisc0128.htm>. For a recent empirical analysis finding increased antibiotic consumption with free programs, see Shanjun Li & Ramanan Laxminarayan, *Are Physicians' Prescribing Decisions Sensitive to Drug Prices? Evidence from a Free-Antibiotics Program* (May 1, 2010) (working paper, available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1598804).

39. James Love, *Prizes, Not Prices, To Stimulate Antibiotic R&D*, SCI. & DEV. NETWORK, Mar. 26, 2008, <http://www.scidev.net/en/opinions/prizes-not-prices-to-stimulate-antibiotic-r-d.html>.

40. James Love & Tim Hubbard, *The Big Idea: Prizes To Stimulate R&D for New Medicines*, 82 CHI.-KENT L. REV. 1519 (2007); James Love & Tim Hubbard, *Prizes for Innovation of New Medicines and Vaccines*, 18 ANNALS HEALTH L. 155 (2009); see also LAXMINARAYAN ET AL., *supra* note 15; MOSSIALOS ET AL., *supra* note 14; SWEDISH PRESIDENCY OF THE EUROPEAN UNION, *supra* note 16; Amy Kapczynski, *Innovation Policy for a New Era*, 37 J.L. MED. & ETHICS 264 (2009) (suggesting prizes for antibiotic development); Kesselheim & Outtersson, *supra* note 25. *But see* Donald W. Light, *Making Practical Markets for Vaccines*, 2 PLOS MED. e271 (2005), available at http://www.who.int/intellectualproperty/submissions/CGD-PLOS-Light-10%1371_journal%pmed%200020271-p-L.pdf (arguing against advanced market commitments in vaccine R&D).

41. AIDAN HOLLIS & THOMAS POGGE, *THE HEALTH IMPACT FUND: MAKING NEW MEDICINES ACCESSIBLE FOR ALL* (2008); Thomas Pogge, *Human Rights and Global Health: A Research Program*, 36 METAPHILOSOPHY 182 (2005); Aidan Hollis, *An Efficient Reward System for Pharmaceutical Innovation* (Jan. 17, 2005) (working paper, available at <http://econ.ucalgary.ca/fac-files/ah/drugprizes.pdf>).

sponsors obtain enhanced financial rewards only if antibiotic conservation targets are met. With this condition in place, a financial incentive would be created for the first time to manage antibiotics for public health rather than just private gain. This second element is necessarily linked to the first: absent this conditionality, increased reimbursement for antibiotics would simply accelerate the patent holder's incentives to aggressively sell the drugs. Taken together, our goal is to pay more for fewer pills consumed. For a simplified example, if a company currently sells one-hundred million antibiotic pills for \$1 each, their total revenue is \$100 million. Under ACE, assume that actual clinical needs with conservation are only fifty million pills. At this point, the company has lost \$50 million in decreased unit sales. But if the company meets the conservation targets, an ACE prize of perhaps \$150 million will be paid—essentially quadrupling the unit price while halving the unit sales. The companies will profit significantly by achieving public health goals.

This conditionality also offers interesting opportunities for special prizes for a few particularly valuable antibiotics. For example, the United States could create a Strategic Antibiotic Reserve to reward the conservation of important antibiotics. Under the present patent-based system, companies turn a profit only if they sell vast quantities of an antibiotic. For drugs in the Strategic Antibiotic Reserve, companies would be rewarded today for *not selling* the antibiotic, preserving a precious resource for dire future needs.⁴²

Third, the biology of resistance creates unique horizontal and vertical coordination problems, even with perfect information and improved incentives at the individual company level. Overuse of antibiotics can create resistance to other drugs in their class. If multiple drug companies hold the patents for these drugs, the companies will need to coordinate some of their market activities for long-term sustainability. For these horizontal coordination activities, limited antitrust waivers will permit efficient market coordination, without some of the monopolistic concerns ordinarily addressed by antitrust law. Limited waivers in other aspects of the law, such as the Stark anti-self-referral legislation, may be required to permit vertical coordination with hospitals, physicians, and other providers in implementing infection control measures.

42. We articulate the Strategic Antibiotic Reserve separately because the unit sales might be extremely low in the first decade after introduction, swamping the insurance reimbursement system with pills with an imputed unit cost in the millions of dollars. In this case, a direct payment mechanism is indicated. The concept of compensating developers for better managing their public good products has a long history in American markets, particularly in agriculture. *See, e.g.*, Agricultural Adjustment Act of 1933, Pub. L. No. 73-10, 41 Stat. 31 (1933) (seeking to decrease supplies of crops during the New Deal era by paying farmers to produce less).

Finally, public funding through the National Institutes of Health (NIH) and other agencies is necessary because for-profit companies do not invest in certain types of research that are essential for public health, including investments in human infrastructure to build research capacities in infectious diseases.

This Article proceeds in six sections. Section I briefly reviews the medical literature on antibacterial resistance. Section II examines the current state of antibiotic research and development. Section III reviews existing legal paradigms for creating and managing antibiotics. Section IV presents our core proposals, the Antibiotic Conservation and Effectiveness (ACE) program. In Section V, we take up critiques of ACE incentives, including the difficulties in fine-tuning financial and reimbursement incentives and the increased investment necessary to make ACE a reality. One key to this proposal is that the patent system remains unchanged; any alternatives offered are contractual and voluntary at the discretion of the companies. We then offer our conclusions in Section VI. The ACE program is designed to improve antibiotic markets, using government contracts to create a long-term and sustainable balance between the supply and demand for antibiotics. The ACE program will better align private and social values in this important sector. Otherwise, we cannot be certain that effective antibiotics will be available when infections strike.

I. ANTIBIOTIC RESISTANCE

The first commercial use of penicillin in the 1940s signaled the birth of the antibiotic era.⁴³ Despite the efficacy of these new antibiotics, the medical community observed the emergence and spread of antibiotic-resistant bacteria within a few years of the introduction of penicillin.⁴⁴ Microorganisms have been found to exhibit a number of biological adaptations, including natural selection of new mutations and the passage of elements carrying resistance genes between species.⁴⁵ Resistant microorganisms pass readily among people, and even more readily among the sickest people in hospitals or other health care delivery institutions.⁴⁶ Antibiotic use can also spur infection by clearing commensal

43. Charles M. Grossman, *The First Use of Penicillin in the United States*, 149 ANNALS INTERNAL MED. 135 (2008).

44. See Mary Barber, *Staphylococcal Infection Due to Penicillin-Resistant Strains*, 2 BMJ 863, 864 (1947) (noting that the first report of penicillin-resistant staphylococcal infections came shortly after the widespread use of penicillin).

45. See generally Marc Lipsitch & Matthew H. Samore, *Antimicrobial Use and Antimicrobial Resistance: A Population Perspective*, 8 EMERGING INFECTIOUS DISEASES 347 (2002).

46. See J. Kristie Johnson et al., *The Role of Patient-to-Patient Transmission in the Acquisition of Imipenem-Resistant Pseudomonas Aeruginosa Colonization in the Intensive Care Unit*, 200 J.

species that serve as natural limits on the overgrowth of deadly bacteria such as *Clostridium difficile*.⁴⁷

Over the past decades, however, we have learned that the way antibiotics are used facilitates the development and spread of resistance.⁴⁸ Sir Alexander Fleming, who shared the Nobel Prize for the discovery of penicillin, first noted the role that antibiotic misuse plays in resistance, reporting, “It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them.”⁴⁹ Misuse of antibiotics occurs in a number of ways, including prescription of antibiotics when they are not needed, prescription of the wrong type of antibiotic, and improper use of antibiotics by patients. All of these factors have direct biological ramifications; one model is that as the most susceptible bacteria are killed, microbes that may have developed resistance mutations can flourish in an environment with fewer competitors.⁵⁰

There is a large literature on factors contributing to the social misuse of antibiotics.⁵¹ One driver is physicians’ prescribing practices. Studies show that physicians vary broadly in their antibiotic prescription practices,⁵² and may not be aware of or adhere to clinical practice guidelines addressing proper use of antibiotic agents.⁵³ For example, studies have shown that generalists and infectious disease specialists were more likely to prefer newer, broader-spectrum drugs for the treatment of community-acquired pneumonia compared to older,

INFECTIOUS DISEASE 900 (2009).

47. See Outterson, *supra* note 18,,for a full discussion of the pathogenesis of *Clostridium difficile*.

48. See generally Saver, *supra* note 32.

49. A. Mark Joffe, *Desperate Therapies and the Amazing Race for Antimicrobial Alternatives*, 17 CAN. J. INFECTIOUS DISEASES MED. & MICROBIOLOGY 285 (2006) (quoting Sir Alexander Fleming, Nobel Prize Acceptance Speech, 1945).

50. See Lipsitch & Samore, *supra* note 45, at 349.

51. See, e.g., McDonnell Norms Group, *Antibiotic Overuse: The Influence of Social Norms*, 207 J. AM. C. SURGEONS 265 (2008). This is true of both pediatric and adult patients. See, e.g., Howard Bauchner et al., *Parents, Physicians, and Antibiotic Use*, 103 PEDIATRICS 395 (1999); see also John Macfarlane et al., *Influence of Patients’ Expectations on Antibiotic Management of Acute Lower Respiratory Tract Illness in General Practice: Questionnaire Study*, 315 BMJ 1211 (1997).

52. Ethan A. Halm et al., *What Factors Influence Physicians’ Decisions to Switch from Intravenous to Oral Antibiotics for Community-Acquired Pneumonia?*, 16 J. GEN. INTERNAL MED. 599 (2001).

53. Galen E. Switzer et al., *Physician Awareness and Self-Reported Use of Local and National Guidelines for Community-Acquired Pneumonia*, 18 J. GEN. INTERNAL MED. 816 (2003).

more narrowly tailored agents still recommended by national guidelines.⁵⁴ Use of broad-spectrum antibiotic agents in patients whose infections are susceptible to a narrower-spectrum product can promote resistance and ultimately impede management if a more severe multidrug-resistant infection develops that requires the broad-spectrum agent.⁵⁵

Patient behavior also contributes substantially to the development of antibiotic resistance. Patients may demand antibiotic agents in inappropriate clinical situations.⁵⁶ Patient demand for antibiotics in the setting of viral or non-infectious diseases can promote resistance, as studies have shown that prescription of multiple courses of the same antibiotic selects for more resistant organisms⁵⁷ and clears ecological space for transmission and growth of resistant pathogens.⁵⁸ Yet patient demand is a leading predictor of whether physicians provide an antibiotic prescription.⁵⁹ In addition, studies have shown that patients are insufficiently aware of the important ramifications of antibiotic overuse in the development of resistance.⁶⁰ Patients also may not always adhere to full treatment lengths,⁶¹ which might be better if the prescription was inappropriate in the first instance. For some infections with particularly dangerous public health implications, such as multidrug-resistant tuberculosis, directly observed therapy (DOT) programs have been employed to ensure patient adherence to a full course of treatment.⁶²

54. See, e.g., Joel Lexchin, *Promoting Resistance?*, 28/29 ESSENTIAL DRUGS MONITOR 11 (2000); Joshua P. Metlay et al., *Tensions in Antibiotic Prescribing: Pitting Social Concerns Against the Interests of Individual Patients*, 17 J. GEN. INTERNAL MED. 87 (2002).

55. Carlos G. Grijalva et al., *Antibiotic Prescription Rates for Acute Respiratory Tract Infections in US Ambulatory Settings*, 302 JAMA 758 (2009).

56. Samuel Coenen et al., *Antibiotic Prescribing for Acute Cough: The Effect of Perceived Patient Demand*, 56 BRIT. J. GEN. PRAC. 183 (2006).

57. Céire Costelloe et al., *Effect of Antibiotic Prescribing in Primary Care on Antimicrobial Resistance in Individual Patients: Systematic Review and Meta-Analysis*, 340 BMJ c2096 (2010).

58. See Phillip Toltzis et al., *Impact of Amoxicillin on Pneumococcal Colonization Compared with Other Therapies for Acute Otitis Media*, 24 PEDIATRIC INFECTIOUS DISEASE J. 24 (2005).

59. See Coenen et al., *supra* note 56.

60. See Jodi Vanden Eng et al., *Consumer Attitudes and Use of Antibiotics*, 9 EMERGING INFECTIOUS DISEASES 1128 (2003); see also Edward A. Belongia et al., *Antibiotic Use and Upper Respiratory Infections: A Survey of Knowledge, Attitudes, and Experience in Wisconsin and Minnesota*, 34 PREVENTATIVE MED. 346 (2002).

61. See Diana I. Brixner, *Improving Acute Otitis Media Outcomes Through Proper Antibiotic Use and Adherence*, 11 AM. J. MANAGED CARE S202 (2005).

62. A. M. Nyamathi et al., *A Randomized Controlled Trial of Two Treatment Programs for Homeless Adults with Latent Tuberculosis Infection*, 10 INT'L J. TUBERCULOSIS & LUNG DISEASE 775 (2006).

External social pressures also contribute to antibiotic overuse and resistance. Direct-to-physician advertising of antibiotics is one such factor. One study of advertisements related to antibiotics in medical journals showed that these advertisements, in promoting use of their products, rarely mentioned the risk of antibiotic resistance.⁶³ The power of such advertising to affect physician-prescribing practices is well documented and will be discussed in more detail in Section IV below. The example of free antibiotic programs combines elements of physician, patient and social pressures to prescribe. As Li and Laxminarayan have recently shown, free antibiotic programs at large U.S. pharmacies, such as Wal-Mart, influence physician prescribing patterns in statistically significant ways.⁶⁴ These market forces are barriers to optimal antibiotic use, but are also important potential levers for the proposed ACE Program. If drug companies were properly incentivized for public health goals, their influence and financial resources could be deployed to counteract many of the clinically inappropriate uses described above. At the very least, the companies would no longer have strong financial incentives to oppose public health conservation measures.

II. THE LIMITATIONS OF NEW ANTIBIOTIC DEVELOPMENT

In recent years, infectious disease experts have expressed concern over the diminishing pipeline of additional antibiotics available to manage resistant disease.⁶⁵ In this Section, we examine the evidence and conclude that new production alone is unlikely to meet clinical needs unless a strong emphasis is also placed on antibiotic conservation.

The Infectious Diseases Society of America (IDSA) has described a consistent decline in the total number of new antibacterial agents approved in the last twenty-five years, and has reported that since 2004, only five systemic agents were actively being developed by the largest pharmaceutical companies.⁶⁶ This is

63. Jacob Gilad et al., *Antibiotic Drug Advertising in Medical Journals*, 37 SCANDINAVIAN J. INFECTIOUS DISEASE 910 (2005).

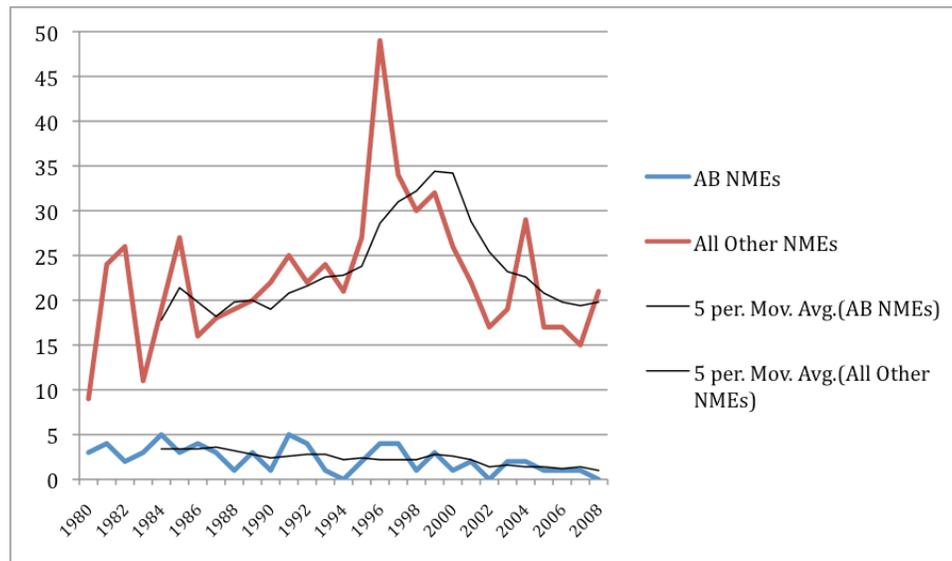
64. Shanjun Li & Ramanan Laxminarayan, *Are Physicians' Prescribing Decisions Sensitive to Drug Prices? Evidence from a Free-Antibiotics Program* (May 1, 2010) (working paper, available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1598804); see also Caffarini, *supra* note 38; Franco et al., *supra* note 38, at 1.

65. See, e.g., BAD BUGS, *supra* note 9; Brad Spellberg et al., *Trends in Antimicrobial Drug Development: Implications for the Future*, 38 CLINICAL INFECTIOUS DISEASES 1279 (2004).

66. David M. Livermore, *Has the Era of Untreatable Infections Arrived?*, 64 J. ANTIMICROBIAL CHEMOTHERAPY i29 (Supp. 1, 2009) (noting that we may have exhausted all therapeutic options); Brad Spellberg et al., *The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America*, 46 CLINICAL

partially a secular trend, as FDA approvals in general have declined in recent years as well, as shown in Figure 1. Part of the problem lies with drug innovation in general, not antibiotics in particular.

FIGURE 1: NUMBER OF ANTIBACTERIAL (AB) AND ALL OTHER NEW MOLECULAR ENTITIES (NMEs) APPROVED BY THE FDA, BY YEAR OF APPROVAL⁶⁷



According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the oxazolidinone class of antibiotics, which includes linezolid (Zyvox), is the only class with a completely novel mode of action that has been developed in the past three decades.⁶⁸ This claim, however, depends on

INFECTIOUS DISEASES 155, 158 (2008). *But see* Julian Davies, *The Garden of Antimicrobial Delights*, 2 F1000 BIOLOGY REPORTS 26 (2010) (suggesting that additional antibiotic development should not be too difficult).

67. Rosa Rodriguez-Monguio, Enrique Seoane-Vasquez, John H. Powers, and Kevin Outterson, Analysis of Systemic Antibiotics Approved in the U.S. Between 1980 and 2009 (2010) (abstract for 138th APHA Annual Meeting, on file with author).

68. Ragnar S. Norrby et al., *Lack of Development of New Antimicrobial Drugs: A Potential Serious Threat to Public Health*, 5 LANCET INFECTIOUS DISEASES 115, 116 (2005). Linezolid is the first member of the oxazolidinone family to be marketed in the United States.

how the term “class” is defined and the time period selected for comparison.⁶⁹ Since 2000, two new antibiotic classes (analogues of classes)⁷⁰—ketolides⁷¹ and glycylicyclines⁷²—have been approved that comprise important variations on old classes with improvements in their activity against resistant organisms. The FDA has also approved daptomycin (Cubicin) and quinupristin/dalfopristin (Synercid) in the last decade. Both of these products feature relatively novel mechanisms of action and could be considered new classes in humans, although prior animal use of virginiamycin has potentially affected quinupristin/dalfopristin. Several researchers have suggested that the proper category is not chemical class, but “functional resistance groups,” drugs for which certain species exhibit patterns of cross-resistance.⁷³ On that basis, the FDA has approved 2-5 new functional resistance groups in the past decade, depending on whether a narrow or expansive definition is used.

A more clinical way to view the success of antibiotic development may be to look at whether we are able to treat patients fighting serious resistant infections. From that perspective, current treatments are improving against some pathogens but worsening against others.⁷⁴ An IDSA task force surveyed the literature and identified six particularly dangerous groups of microorganisms displaying increasing resistance rates that pose important threats to patient care: extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and

69. *Longer Antimicrobial Patents*, *supra* note 24.

70. Many independent industry experts would not consider ketolides and glycylicyclines as new classes, but as “analogues of existing classes.” Interview with Ursula Theuretzbacher, Founder, Ctr. for Anti-Infective Agents (July 27, 2010) (on file with Kevin Outterson).

71. Telithromycin (Ketek) is a novel derivative of the class of macrolide antibiotics that was designed with side-chain modifications intended to overcome antibiotic resistance to other macrolides. Kimberly D. Clay et al., *Severe Hepatotoxicity of Telithromycin: Three Case Reports and Literature Review*, 142 ANNALS INTERNAL MED. 415 (2006). Notably, telithromycin was not demonstrated to be more effective than other antibiotics in treating the infectious diseases for which it was indicated. It is also currently available only in oral form, which limits its utility in the sickest of patients with multidrug resistant infections.

72. Tigecycline (Tygacil) is derivative of the class of tetracyclines with microbiological activity against intra-abdominal and skin and soft tissue infections caused by susceptible or multidrug-resistant staphylococci, enterococci, or streptococci as well as most *Enterobacteriaceae* and anaerobic pathogens. Ethan Rubinstein & David Vaughan, *Tigecycline: A Novel Glycylicycline*, 65 DRUGS 1317 (2005).

73. LAXMINARAYAN ET AL., *supra* note 15, at 20, 40-41; MOSSIALOS, *supra* note 14, at 7, 113.

74. Livermore, *supra* note 66.

Aspergillus.⁷⁵ The IDSA concluded that among these six priority groups of pathogens, MRSA has the largest current clinical impact and also the largest market for drugs.⁷⁶ Not surprisingly, a number of potentially useful MRSA drugs are in late-stage development.⁷⁷ The other five priority pathogens with smaller potential markets have fewer new agents in the pipeline,⁷⁸ which is not unexpected given market incentives.

The primary reason that pipelines for some priority pathogens can be so small is that for-profit companies with very high revenue expectations have dominated pharmaceutical research and development (R&D). The average funding for pharmaceutical R&D by the National Institutes of Health (NIH) has risen more slowly over time⁷⁹ as compared to pharmaceutical manufacturers.⁸⁰ More significantly, for-profit companies control approximately 90% of drug-related patents,⁸¹ which often cover underlying research performed in academic institutions supported by public funds.⁸² Though these companies have contributed to important progress in development of new medical treatments,⁸³ they also are beholden to their shareholders. Data from the Securities and Exchange Commission and the Department of Health and Human Services in the late 1990s suggest that the largest pharmaceutical manufacturers invest about one-third of their revenues in sales and general administration (including advertising), another 20% in return to shareholders, and about 15% in R&D in 2000⁸⁴ (industry estimates report 17% in 2009).⁸⁵ More recent data suggest that

75. George H. Talbot et al., *Bad Bugs Need Drugs: An Update on the Development Pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America*, 42 *CLINICAL INFECTIOUS DISEASES* 657, 657 (2006).

76. *Id.*

77. *Id.*

78. *Id.*

79. See NAT'L SCI. FOUND., *FEDERAL FUNDS FOR RESEARCH AND DEVELOPMENT: FISCAL YEARS 2007-09* (2010), available at <http://www.nsf.gov/statistics/nsf10305>.

80. CONG. BUDGET OFFICE, *RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY* (2006), available at <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>.

81. Aaron S. Kesselheim & Jerry Avorn, *Using Patent Data To Assess the Value of Pharmaceutical Innovation*, 37 *J.L. MED. & ETHICS* 176, 179 (2009).

82. Aaron S. Kesselheim & Jerry Avorn, *University-Based Science and Biotechnology Products: Defining the Boundaries of Intellectual Property*, 293 *JAMA* 850 (2005).

83. JOHN L. LAMATTINA, *DRUG TRUTHS: DISPELLING THE MYTH ABOUT PHARMA R&D* (Wiley 2008).

84. FAMILIES USA, *OFF THE CHARTS: PAY, PROFITS AND SPENDING BY DRUG COMPANIES* (2001), available at www.familiesusa.org/assets/pdfs/offthecharts6475.pdf; KAISER FAMILY FOUND., *PRESCRIPTION DRUG TRENDS: A CHARTBOOK* 65, 70 fig. 4.5, 71 fig. 4.6 (2000), available at <http://www.kff.org/rxdrugs/3019-index.cfm>; Press Release, Public Citizen's Congress Watch, Drug

pharmaceutical manufacturers still spend 31%-50% of sales on marketing.⁸⁶ While industry supporters offer slightly different numbers,⁸⁷ the essential point is clear: increased sales of pharmaceuticals translate into only a limited increase in R&D after accounting for other expenses and R&D costs bear little relationship to prices. As Professor Scherer notes: “Sunk research-and-development costs are bygones and are therefore irrelevant in current pricing decisions.”⁸⁸

As a result, projected revenue, rather than other factors such as morbidity of a disease or perceived public health need, can become the most important determinant of new drug development.⁸⁹ Antibiotics face unique reimbursement challenges in part because of their history of low unit prices, but also because the total unit sales may be smaller than other drug markets.⁹⁰ From a financial point of view, drug companies often disparage antibiotics as poor sellers due to the

Industry Most Profitable Again (April 11, 2001), available at <http://www.citizen.org/pressroom/release.cfm?ID=819> (noting that in 2000 Fortune 500 drug companies devoted 30% of revenues to marketing and administration and 12% to R&D).

85. PHARM. RESEARCH AND MFRS. OF AM., PHARMACEUTICAL INDUSTRY PROFILE 2009 (2009), available at <http://www.phrma.org/files/attachments/PhRMA%202009%20Profile%20FINAL.pdf> (citing 17.4% of total sales into R&D).

86. Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLoS MED. 29, 32 (2008), <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pm.ed.0050001>. (finding that the actual amount of promotional expenditures “could range from a low of US\$27.7 billion to a high of US\$57.5 billion”).

87. See *R&D Investment by US Biopharma Remains Strong Despite Ongoing Economic Challenges, Reaching a Record \$65.3 Billion*, THE PHARMA NEWS, Mar. 17, 2010, available at http://www.phrma.org/news/news/rd_investment_us_biopharmaceutical_companies_remains_strong_despite_ongoing_economic_chall (reporting that the pharmaceutical industry trade group estimates that “the USA’s pharmaceutical research companies have consistently invested around 18% of domestic sales on R&D activities”).

88. F.M. Scherer, *The Pharmaceutical Industry – Prices and Progress*, 351 NEW ENG. J. MED. 927, 929 (2004).

89. As Roin has pointed out, this perspective has a substantial effect on decisions regarding whether to continue to invest in “pipeline” drugs. Companies have preferentially invested in research on products whose intellectual property ownership is clear (or solidly under their control), excluding research on other approaches or agents that could be better suited to address unmet public health needs. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503 (2009). *But see* Kevin Outterson, *Death from the Public Domain?*, 87 TEXAS L. REV. SEE ALSO 45 (2009), <http://www.texasrev.com/seealso/volume-87/roin/death-from-the-public-domain.html> (challenging the example of an unpatentable drug given by Roin).

90. Richard P. Wenzel, *The Antibiotic Pipeline—Challenges, Costs, and Values*, 351 NEW ENG. J. MED. 523 (2004).

short courses of therapy, which limit the ability to earn revenues over a long period of time.⁹¹ “Blockbuster” drugs are usually defined as those producing revenues in excess of a billion dollars per year,⁹² but in antibiotics, companies would consider \$200 million in annual sales to be a successful market.⁹³ And while some large pharmaceutical companies are moving away from the blockbuster drug development model,⁹⁴ many manufacturers still focus on diseases that may provide a higher return on investment.⁹⁵ Even when drug companies decide to invest in R&D for antibiotics, they are drawn to the largest markets, such as the multibillion-dollar MRSA market. Large multinational drug companies have not deeply invested in finding drugs for the other five priority pathogens identified by the IDSA.⁹⁶ The ACE program redirects company R&D incentives by instituting value-based reimbursement. Companies will be paid for the health impact of their antibiotic, not the historically low prices prevalent today.

Other peculiar factors also may disincentivize investment in new antibiotic development by for-profit companies. Increasing resistance makes the antibiotic less effective over time, which might limit the ability of pharmaceutical manufacturers to use standard “life-cycle management” strategies, such as the creation of variant dose or extended-release formulations.⁹⁷ Existing evidence

91. Roger Finch & Pamela A. Hunter, *Antibiotic Resistance—Action To Promote New Technologies: Report of an EU Intergovernmental Conference Held in Birmingham, UK, 12-13 December 2005*, 58 J. ANTIMICROBIAL CHEMOTHERAPY, i3, 17 (2006).

92. Bruce Booth & Rodney Zimmel, *Quest for the Best*, 2 NATURE REV. DRUG DISCOVERY, 838, 838 (2003).

93. Interview with Ursula Theuretzbacher, Founder, Ctr. for Anti-Infective Agents (July 27, 2010) (on file with Kevin Outterson).

94. See David M. Cutler, *The Demise of the Blockbuster?*, 356 NEW ENG. J. MED. 1292 (2007); see also Matthew Goodman, *New Boss Andrew Witty Revamps GlaxoSmithKline*, THE TIMES, Jul. 27, 2008, http://business.timesonline.co.uk/tol/business/industry_sectors/industrials/article4405862.ece.

95. Steven J. Projan, *Why Is Big Pharma Getting Out of Antibacterial Drug Discovery?*, 6 CURRENT OPINION IN MICROBIOLOGY 427, 428 (2003).

96. Fortunately, smaller pharmaceutical companies have taken the lead in research and development where larger manufacturers have stepped out. Andriy Luzhetskyy et al., *The Future of Natural Products as a Source of New Antibiotics*, 8 CURRENT OPINION INVESTIGATIVE DRUGS 608 (2007). For example, daptomycin was shepherded to approval in 2004 by the Boston-based biotech company Cubist seven years after Eli Lilly closed development of the product. Lilly outlicensed daptomycin early in its clinical trials owing to reports of side effects, but Cubist later determined that the side effects were related to suboptimal dosing strength and intervals. John F. Barrett, *Can Biotech Deliver New Antibiotics?*, 8 CURRENT OPINION IN MICROBIOLOGY 498 (2005).

97. See Edward Power, *Impact of Antibiotic Restrictions: The Pharmaceutical Perspective*, 12

suggests that commercially significant resistance does not occur during the patent term, so this effect may be modest.⁹⁸

The market for new antibiotic products in the United States and other wealthy countries is limited by public health efforts to prevent infections and restrict the prescription of antibiotics in order to prevent the acceleration of bacterial resistance.⁹⁹ Pharmaceutical companies are concerned that important new antibiotic drugs may be subject to aggressive restrictions on use, price controls, and copying by unlicensed generic manufacturers in developing countries.¹⁰⁰ These programs may greatly improve public health, but they reduce the demand for antibiotics and thus shrink the market for the companies that sell them. Antibiotic conservation directly threatens the commercial market for new antibiotics.¹⁰¹ Similarly, the production of multiple new antibiotics promoted by for-profit companies directly threatens conservation. The ACE program directly addresses this problem by reimbursing for conservation.

Finally, drug companies sometimes claim that antibiotics face uniquely higher research costs that discourage development.¹⁰² For example, critics claim that FDA regulatory requirements have been overly burdensome in the field of infectious diseases, where placebo-controlled studies can be infeasible and alternative study designs, such as non-inferiority studies, can be challenging and costly to organize.¹⁰³ While these claims about clinical study designs are plausible, they are not universally accepted.¹⁰⁴ Antibiotic clinical trials are often less expensive than many other types of drug trials because many “predictive animal models [are] available and the late attrition rate due to ineffectiveness is low for antibiotics.”¹⁰⁵ In addition, speeding up antibiotic approvals may increase

CLINICAL MICROBIOLOGY & INFECTION 25, 27 (2006).

98. See *Legal Ecology of Resistance*, *supra* note 19, at 637-41.

99. See Spellberg et al., *supra* note 65; Spellberg et al., *supra* note 66.

100. Projan, *supra* note 95, at 428.

101. *Legal Ecology of Resistance*, *supra* note 19, at 642-45.

102. David M. Shlaes, *The Abandonment of Antibacterials: Why and Wherefore?*, 3 CURRENT OPINION PHARMACOLOGY 470 (2003).

103. Cecilia H. Burke & Geoffrey M. Levitt, *A Manufacturer's Perspective: Recent Challenges in Antibiotic Drug Approval*, 2 UPDATE: FOOD & DRUG L. REG. & ED. 12 (2008).

104. GOVERNMENT ACCOUNTABILITY OFFICE, NEW DRUG APPROVAL: FDA'S CONSIDERATION OF EVIDENCE FROM CERTAIN CLINICAL TRIALS (2010), available at <http://www.gao.gov/new.items/d10798.pdf> (discussing issues with non-inferiority trials for antibiotics); Kevin Outterson, John H. Powers III, Ian M. Gould & Aaron S. Kesselheim, *Questions About the 10 X '20 Initiative*, 51 CLINICAL INFECTIOUS DISEASES 751 (2010).

105. Interview with Ursula Theuretzbacher, Founder, Ctr. for Anti-Infective Agents (July 27, 2010) (on file with Kevin Outterson).

the risk that antibiotics reach the market with unknown safety risks.¹⁰⁶ In the past three decades, drug companies have withdrawn numerous antibiotics with safety concerns from the U.S. market, more than any other drug class.¹⁰⁷ This is not a record that supports a call for weaker safety standards. Enhanced conservation under ACE will diminish the urge to rush antibiotics through trials prematurely.

In recent years, many groups have suggested proposals to address the problem of serious disease from resistant pathogens.¹⁰⁸ Some proposals focus on reducing demand for antibiotics, for example, through conservation, appropriate use, antibiotic stewardship and infection control (see Sector 3 in Table 1).¹⁰⁹ Others focus on the supply side (Sectors 2, 4 and 6), generally suggesting additional property rights or financial incentives to encourage for-profit pharmaceutical industry investment in new drug development.¹¹⁰ The better discussions, in our view, integrate both conservation and production into a coherent policy analysis.¹¹¹ In the next Part, we analyze the most prominent conservation and production proposals and consider how they align financial incentives with public health goals. Our proposals borrow from many existing ideas, but integrate them simultaneously to address both conservation and production.

III. EXISTING PARADIGMS TO PROMOTE CONTINUED ANTIBIOTIC EFFECTIVENESS

Proposals to address the growing problem with resistant microorganisms have emerged from a number of different perspectives. In many cases, these proposals come from different academic disciplines, often operating independently of each other. Patent lawyers suggest patent extensions; epidemiologists suggest infection control; clinicians demand new antibiotics; drug companies want to maximize revenue; and regulators suggest new regulations. These disciplines must break their isolation and integrate their perspectives into a comprehensive solution.

First, many researchers have emphasized conservation of currently available antibiotics through strategies such as infection control, as well as limitations on the use of antibiotics to clinically appropriate situations. One institutional

106. *Id.*

107. Rodriguez-Monguio et al., *supra* note 67.

108. *See supra* notes 9-16 and accompanying text.

109. *See, for example, the work of the Alliance for the Prudent Use of Antibiotics, supra* note 10.

110. *See, for example, the report by the Infectious Diseases Society of America, supra* note 9.

111. *See, e.g., LAXMINARAYAN ET AL., supra* note 15; MOSSIALOS ET AL., *supra* note 14; NUGENT, BACK & BEITH, *supra* note 13

champion of this Sector 3 (see Table 1) approach is the Alliance for the Prudent Use of Antibiotics (APUA). Other strategies focus on developing new drugs rather than conservation of existing ones. For example, the IDSA has prominently aligned itself with a call for new financial incentives to support the development of new antibiotic pharmaceutical products. These Sector 2 proposals include additional patent-based exclusivity for sponsors.¹¹² Some academics and think tanks have suggested non-patent-based incentive proposals, including guaranteed purchase contracts or cash prizes¹¹³ for successful development of a new antibiotic.¹¹⁴ These are Sector 6 proposals, focused on contract rather than property rights. The IDSA and others have proposed reducing costs of antibiotic research and development (Sector 4), which can include changing regulatory parameters that guide new drug approval.¹¹⁵ IDSA has also supported increasing government grants to build the infrastructure and help promote better understanding of basic biology and drug targets (Sector 6).¹¹⁶ Tort law could also be used, either as a liability threat to promote conservation (Sector 7) or as a shield to promote production of new drugs by preempting state tort law (Sector 8). We will first examine the major existing efforts before we turn to our novel proposals.

A. Antibiotic Conservation

Environmental infection control¹¹⁷ and programs designed to promote rational use of antibiotics (also called “antibiotic stewardship”)¹¹⁸ are the primary

112. See BAD BUGS, *supra* note 9. But when IDSA supported legislation in the 111th Congress, the proposed legislation did not include the controversial patent language. See Strategies To Address Antimicrobial Resistance Act, H.R. 2400, 111th Cong. (1st Sess. 2009).

113. See, e.g., LAXMINARAYAN ET AL., *supra* note 15; MOSSIALOS ET AL., *supra* note 14; SWEDISH PRESIDENCY OF THE EUROPEAN UNION, *supra* note 16; Kapczynski, *supra* note 40 (suggesting prizes for antibiotic development); Love & Hubbard, *The Big Idea*, *supra* note 40, at 1519; Love & Hubbard, *Prizes for Innovation*, *supra* note 40, at 155; Kesselheim & Outtersson, *supra* note 25. But see Light, *supra* note 40, at e271 (arguing against advanced market commitments in vaccine R&D).

114. Love, *supra* note 40.

115. BAD BUGS, *supra* note 9; Projan & Shlaes, *supra* note 35.

116. *Id.*

117. M. Lindsay Grayson et al., *Significant Reductions in Methicillin-Resistant Staphylococcus Aureus Bacteraemia and Clinical Isolates Associated with a Multisite, Hand Hygiene Culture-Change Program and Subsequent Successful Statewide Roll-Out*, 188 MED. J. AUSTRAL. 633 (2008).

118. Allison E. Aiello et al., *Ethical Conflicts in Public Health Research and Practice: Antimicrobial Resistance and the Ethics of Drug Development*, 96 AM. J. PUB. HEALTH 1910

mechanisms through which antibiotic conservation is currently implemented.¹¹⁹ Infection control is a public health measure that can help slow the spread of all infections, including particularly virulent or resistant microbes.¹²⁰ Examples of infection control mechanisms include tuberculosis testing for healthcare professionals,¹²¹ environmental cleaning,¹²² screening of high-risk patients for resistant microbes,¹²³ and isolating high-risk patients in special rooms or wards.¹²⁴

Antibiotic stewardship can involve physician education or active management of physicians' prescription of antibiotics to encourage the appropriate selection, dosing, route, and duration of therapy.¹²⁵ The goal is to optimize clinical outcomes while minimizing unintended consequences of antibiotic use like the emergence of resistance.¹²⁶ Academic detailing programs¹²⁷ and antibiotic prescription guidelines¹²⁸ teach physicians about evidence-based prescribing without formal restrictions on their prescribing behaviors. Active management of prescription choices is usually a top-down process organized at the level of the payor or practice organization. The most interventionist programs involve formal restrictions on prescribing and can exclude certain antibiotics

(2006).

119. See *Fighting Antibiotic Resistance*, *supra* note 25, at 1691.

120. Rajesh K. Malik et al., *Epidemiology and Control of Vancomycin-Resistant Enterococci in a Regional Neonatal Intensive Care Unit*, 18 PEDIATRIC INFECTIOUS DISEASE J. 352 (1999).

121. Sharon F. Welbel et al., *Protecting Health Care Workers from Tuberculosis: A 10-Year Experience*, 37 AM. J. INFECTION CONTROL 668 (2009).

122. Lynn Eaton, *Hand Washing Is More Important than Cleaner Wards in Controlling MRSA*, 330 BMJ 922 (2005).

123. Walter E. Pofahl et al., *Active Surveillance Screening of MRSA and Eradication of the Carrier State Decreases Surgical-Site Infections Caused by MRSA*, 208 J. AM. C. SURGEONS 981 (2009); Stephan Harbarth et al., *Universal Screening for Methicillin-Resistant Staphylococcus Aureus at Hospital Admission and Nosocomial Infection in Surgical Patients*, 299 JAMA 1149 (2008).

124. Susan A. Maloney et al., *Efficacy of Control Measures in Preventing Nosocomial Transmission of Multidrug-Resistant Tuberculosis to Patients and Health Care Workers*, 122 ANNALS OF INTERNAL MED. 90 (1995).

125. See Saver, *supra* note 32.

126. Timothy H. Dellit et al., *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship*, 44 CLINICAL INFECTIOUS DISEASE 159 (2007).

127. Daniel H. Solomon et al., *Academic Detailing To Improve Use of Broad-Spectrum Antibiotics at an Academic Medical Center*, 161 ARCHIVES OF INTERNAL MED. 1897 (2001).

128. Kristin Schaffer et al., *Do Educational Interventions Improve Management of Patients with Community-Acquired Pneumonia?*, 28 J. HEALTHCARE QUALITY 7 (2006).

from clinical use.¹²⁹ Other less restrictive types of active management include requiring heightened justification from physicians before prescribing certain antibiotics. Prior authorization requirements, for example, have been shown to change prescribing patterns in other drug classes.¹³⁰

Some stewardship tactics, particularly formulary restriction and preauthorization requirements, have demonstrated ability to affect antibiotic resistance rates; one study found that six months after restricting prescribing of vancomycin, colonization by vancomycin-resistant *Enterococcus* (VRE) decreased from 47% to 15% in one hospital.¹³¹ Stewardship programs can also be cost-effective for hospitals¹³² and health care systems.¹³³

Despite these successes, studies have also shown that stewardship programs are not fully effective against the emergence of antibiotic resistance.¹³⁴ Recent systematic reviews concluded that inpatient stewardship programs can reduce antibacterial resistance,¹³⁵ but that similar outcomes are much harder to achieve in the outpatient realm.¹³⁶ MRSA has been documented to circumvent patient isolation in different rooms or across separated cohort bays.¹³⁷ Other stewardship programs, such as educational tools aimed at teaching proper antibiotic use to physicians and disseminating expert-developed clinical guidelines, have varied effects on prescribing practices and have not been shown to have a substantial impact on development of resistance.¹³⁸ Formulary restrictions on certain

129. This is otherwise known as an “exclusive formulary.” See Muhammad Mamdani et al., *Impact of a Fluoroquinolone Restriction Policy in an Elderly Population*, 120 AM. J. MED. 893 (2007).

130. Michael A. Fischer et al., *Medicaid Prior-Authorization Programs and the Use of Cyclooxygenase-2 Inhibitors*, 351 NEW ENG. J. MED. 2187 (2004).

131. John M. Quale et al., *Manipulation of a Hospital Antimicrobial Formulary To Control an Outbreak of Vancomycin-Resistant Enterococci*, 23 CLINICAL INFECTIOUS DISEASE 1020 (1996).

132. Philippe Lesprit & Christian Brun-Buisson, *Hospital Antibiotic Stewardship*, 21 CURRENT OPINION INFECTIOUS DISEASE 344 (2008).

133. Belinda E. Ostrowsky et al., *Control of Vancomycin-Resistant Enterococcus in Health Care Facilities in a Region*, 344 NEW ENG. J. MED. 1427 (2001).

134. Jeroen A. Schouten et al., *Barriers to Optimal Antibiotic Use for Community-Acquired Pneumonia at Hospitals: A Qualitative Study*, 16 QUALITY & SAFETY HEALTH CARE 143 (2007).

135. Peter Davey et al., *Interventions To Improve Antibiotic Prescribing Practices for Hospital Inpatients*, 4 COCHRANE DATABASE SYSTEMATIC REVIEWS CD003543 (2005).

136. Sandra R. Arnold & Sharon E. Straus, *Interventions To Improve Antibiotic Prescribing Practices in Ambulatory Care*, 4 COCHRANE DATABASE SYSTEMATIC REVIEWS CD003539 (2005).

137. Jorge A. Cepeda et al., *Isolation of Patients in Single Rooms or Cohorts To Reduce Spread of MRSA in Intensive-Care Units: Prospective Two-Centre Study*, 365 LANCET 295 (2005).

138. Paula Wilton et al., *Strategies To Contain the Emergence of Antimicrobial Resistance: A Systematic Review of Effectiveness and Cost-Effectiveness*, 7 J. HEALTH SERVICES, RES. & POL'Y

antibiotics have led to over-prescription and increased resistance to other non-restricted antibiotics.¹³⁹ Finally, some studies have shown that even rigorous antibiotic restriction practices that result in short-term improvements and slower overall rates of resistance growth have not fully deterred antibiotic resistance.¹⁴⁰ Conservation buys more time, but is only a partial solution.

The scientific literature on stewardship programs thus suggests that certain sensible and well-coordinated programs can be effective against antimicrobial resistance. However, social factors related to the pharmaceutical and health delivery markets have limited the implementation of effective stewardship and infection control strategies. In particular, we have identified two primary ways that the financial incentives of important actors in this market are misaligned.

First, formulary restrictions and preauthorization requirements can be effective stewardship tools, but pharmaceutical manufacturers generally disfavor such measures since they dampen demand for their products. These managed-care techniques restrict access to their products through tiered formularies or as part of step therapy.¹⁴¹ The industry has fought these restrictions in many ways, including litigation in the highest courts.¹⁴² Since pharmaceutical companies are such powerful institutional actors, any public health program that faces strident drug company opposition will have difficulty succeeding. Our ACE proposals are

111 (2002).

139. James J. Rahal et al., *Class Restriction of Cephalosporin Use To Control Total Cephalosporin Resistance in Nosocomial Klebsiella*, 280 JAMA 1233 (1998).

140. David Livermore, *Can Better Prescribing Turn the Tide of Resistance?*, 2 NATURE REVIEWS MICROBIOLOGY 73 (2004).

141. Pharmacy benefit managers (PBMs), which implement formularies for public and private health insurance plans, are a primary target of manufacturers in this regard. Manufacturers use a combination of rebates and fees to secure more favorable placement on a formulary, including access rebates for placement of products on the PBM formulary and market share rebates for garnering higher market share than established targets. John Carroll, *When Success Sours: PBMs Under Scrutiny*, MANAGED CARE MAGAZINE, Sept. 2002, available at <http://www.managedcaremag.com/archives/0209/0209.pbms.html>.

142. For example, state Medicaid programs offer insurance coverage for low-income patients, but in recent years Medicaid programs have struggled with rising spending on pharmaceutical products. When a number of states experimented with formulary restrictions aimed at reducing drug costs, pharmaceutical manufacturers sued to prevent their implementation. The case ultimately reached the Supreme Court, which held that the states' actions were legal. *Pharm. Research & Mfrs. of Am. v. Walsh*, 123 U.S. 1855 (2003). The drug industry recently lost a similar case before the European Court of Justice, involving formulary tools in the English National Health System. *Case C-62/09, Ass'n of the Brit. Pharm. Indus. v. Med. Healthcare Prod. Regulatory Agency*, 2010 E.C.R. (holding that public authorities may offer financial incentives to physicians who prescribe generics and cheaper therapeutic substitutes).

designed to align private financial incentives with public health goals in a way that makes the drug companies full partners in antibiotic conservation efforts.

Second, hospitals and physicians do not have a billing code for conservation. The lack of both direct reimbursement for infection control and upfront resources to implement stewardship measures effectively have limited infection control measures at hospitals and ambulatory surgical centers.¹⁴³ Budgets for infection control continue to tighten—according to recent Medicare guidelines, hospitals will not be reimbursed for the additional costs of treating inpatients who develop urinary or vascular catheter-associated infections, whether or not the infection was avoidable.¹⁴⁴ Increased financial strain on individual institutions and their budgets for infectious disease programs assures that such programs remain chronically underfunded and underperforming. While some studies have claimed that infection control is cost effective, these studies generally compare hospital costs or charges rather than actual reimbursement.¹⁴⁵ Under Medicare and many private payor reimbursement systems, even these supposedly cost-effective programs probably lose money for the hospital.¹⁴⁶ Infection control is not a revenue center for U.S. hospitals. The U.S. system offers billions of dollars in tax and patent incentives for new antibiotic production, but virtually no market incentives for conservation. Under the ACE program, providers would be rewarded for conservation, either directly through the Medicare reimbursement system or indirectly from drug companies wanting to achieve their own conservation targets.

Finally, hospitals and other health care institutions have little incentive to cooperate regionally to support infection control. Infections pass between hospitals and long-term care facilities, and between rival institutions as patients and other populations circulate. Just as water pollution control is more effective when managed for the entire watershed, infections should be managed on a public health basis, a concept we call *germ shed management*.¹⁴⁷ The Netherlands

143. Michael Edmond & Theodore C. Eickhoff, *Who Is Steering the Ship? External Influences on Infection Control Programs*, 46 CLINICAL INFECTIOUS DISEASES 1746 (2008); Eli N. Perencevich et al., *Raising Standards While Watching the Bottom Line: Making a Business Case for Infection Control*, 28 INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY 1121 (2007); Outterson, *supra* note 18.

144. See Heidi L. Wald & Andrew M. Kramer, *Nonpayment for Harms Resulting From Medical Care: Catheter-Associated Urinary Tract Infections*, 298 JAMA 2782, 2782-84 (2007).

145. See, e.g., Phillipe Lesprit & Christian Brun-Buisson, *Hospital Antibiotic Stewardship*, 21 CURRENT OPINION INFECTIOUS DISEASES 344 (2008) (summarizing a number of studies showing cost savings from antibacterial conservation programs).

146. Outterson, *supra* note 18.

147. Outterson, *supra* note 18.

provides clear evidence that a coordinated approach yields good results.¹⁴⁸ The ACE program facilitates coordination by giving significant financial incentives to the patent holders who operate globally.

In short, infection control and antibiotic stewardship programs sometimes succeed even in the face of the daunting financial incentives and institutions currently standing in opposition. If maintaining antibiotic effectiveness is a public good, then coordination should be facilitated among actors in a position to implement effective conservation, especially the drug companies and health care providers.¹⁴⁹ This is where we believe that the ACE program we propose in Part IV can have a significant impact.

B. Property-Based Incentives

Apart from efforts at infection control and stewardship, some have called for additional patent initiatives intended to increase the supply of antibiotics by encouraging investment in R&D,¹⁵⁰ even though patents as production incentives (Sector 1)¹⁵¹ are only one of eight possible policy solutions to the problem of antibiotic resistance.¹⁵² The patent system, which provides periods of market exclusivity for drug products, has long been the primary mechanism used to encourage for-profit companies to invest in new drug discovery and development in the pharmaceutical field.¹⁵³ Pharmaceutical manufacturers use their market exclusivity period to earn extraordinary revenues on their products.¹⁵⁴ Under the patent system, many important new drug products have been developed and marketed, leading to substantial public health gains, while the research-based pharmaceutical industry has remained a leader in earnings growth and return-on-equity for its shareholders.¹⁵⁵

148. Heiman F. Wertheim et al., *Low Prevalence of Methicillin-Resistant Staphylococcus Aureus (MRSA) at Hospital Admission in the Netherlands: The Value of Search and Destroy and Restrictive Antibiotic Use*, 56 J. HOSPITAL INFECTIONS 321 (2004).

149. Benjamin M. Althouse et al., *A Public Choice Framework for Controlling Transmissible and Evolving Diseases*, 107 PNAS 1696, 1699 (2010).

150. See, e.g., BAD BUGS, *supra* note 9.

151. See Table 1.

152. See *supra* Table 1.

153. See generally J. H. Barton & E. J. Emanuel, *The Patents-Based Pharmaceutical Development Process: Rationale, Problems, and Potential Reforms*, 294 JAMA 2075 (2005).

154. Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193 (2005).

155. CONG. BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY (2006), available at <http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf>.

However, recent studies have revealed important problematic effects of the patent system incentives on public health,¹⁵⁶ and have even questioned whether this system contributes positively to the U.S. economy.¹⁵⁷ The fixed patent term begins when the patent is filed, usually not long after the initial isolation of a new antibiotic molecule. As a result, manufacturers are incentivized to move their products to market as quickly as possible, and regulatory authorities such as the FDA are pressured to approve products as quickly as possible—both of which can lead to missed signals for emerging safety problems.¹⁵⁸ After marketing approval, the fixed patent term encourages manufacturers to maximize their return on investment by promoting rapid uptake of the product. Drug companies have recently paid hefty fines for promoting drugs for conditions not supported on the drug label approved by the FDA.¹⁵⁹ With the patent clock ticking, companies have a clear incentive to maximize revenues before generic competition appears.¹⁶⁰ Such overuse is financially wasteful and can expose patients to risks of adverse events without providing them with the benefits of the drug.¹⁶¹ In the case of antibiotics, overuse is potentially even more troublesome, because it can speed the development and spread of antibiotic resistance.¹⁶² One

156. Aaron S. Kesselheim, *Intellectual Property Policy in the Pharmaceutical Sciences: The Effect of Inappropriate Patents and Market Exclusivity Extensions on the Health Care System*, 9 AAPS J. E306, art. 33 (2007).

157. JAMES BESSEN & MICHAEL J. MEURER, *PATENT FAILURE: HOW JUDGES, BUREAUCRATS AND LAWYERS PUT INNOVATORS AT RISK* (Princeton Univ. Press 2008).

158. Studies have shown that New Drug Applications approved on an accelerated time frame as artificial regulatory deadlines approach are more likely to have safety problems after they are on the market. See Daniel Carpenter et al., *Drug-Review Deadlines and Safety Problems*, 358 NEW ENG. J. MED. 1354 (2008); see also Mary K. Olson, *Are Novel Drugs More Risky for Patients than Less Novel Drugs?*, 23 J. HEALTH ECON. 1135 (2004). Notably, these findings remain controversial. Clark Nardinelli et al., *Letter to the Editor: Drug-Review Deadlines and Safety Problems*, 359 NEW ENG. J. MED. 95 (2008).

159. See Aaron S. Kesselheim, David M. Studdert & Michelle M. Mello, *Whistle-Blowers' Experience in Major Fraud Litigation against Pharmaceutical Companies*, 362 NEW ENG. J. MED. 1832, 1833 (2010) (describing nine cases of illegal off-label marketing leading to over \$3.5 billion in recoveries). See generally Aaron S. Kesselheim & David M. Studdert, *Whistleblower-Initiated Enforcement Actions Against Health Care Fraud and Abuse in the United States, 1996-2005*, 149 ANNALS INTERNAL MED. 342 (2008) (finding increasing numbers of pharmaceutical-related fraud cases).

160. William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays under Medicaid*, 29 HEALTH AFF. 1383 (2010).

161. JERRY AVORN, *POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS* (2004).

162. John B. Horowitz & H. Brian Moehring, *How Property Rights and Patents Affect*

of us has previously characterized this behavior as “patent holder waste” if the patent holder’s overzealous marketing degrades the usefulness of the antibiotic before the patent expires.¹⁶³

With these general comments in mind, we consider a number of different proposals that have been recommended for adjusting the patent-based market exclusivity system to make investment in antibiotic R&D more lucrative to for-profit companies. In large part, we remain critical of these patent-based approaches.¹⁶⁴

1. Patent Extensions

A number of Sector 2¹⁶⁵ (patents as incentives) proposals offer to extend patent or data exclusivity periods for newly approved antibiotics. Patents last for twenty years from the filing date, but due to development and regulatory approval times, the effective market exclusivity life of a newly approved small-molecule drug is usually on the order of eight to fifteen years.¹⁶⁶ The U.S. Government Accountability Office at one time suggested that patents could be lengthened “to 25 or 30 years” for important drugs with “high therapeutic potential,” which would include certain antibiotic products.¹⁶⁷ An alternative proposal that would accomplish similar goals involves starting the patent or market exclusivity term at the time of FDA regulatory approval, rather than when the patent is filed.¹⁶⁸ Longer market exclusivity terms would provide sponsors with more time in which to earn revenues on their products. A few commentators recommend extremely long patent terms as a production incentive and also as a Sector 1¹⁶⁹ conservation device.¹⁷⁰ They suggest that excessive use of antibiotics

Antibiotic Resistance, 13 HEALTH ECON. 575 (2004); Eric Kades, *supra* note 19, at 611-12.

163. See, e.g., *Legal Ecology of Resistance*, *supra* note 19; *Vanishing Public Domain*, *supra* note 19.

164. See Kesselheim & Outtersson, *supra* note 25.

165. See Table 1.

166. Most estimate an effective patent life for small-molecule drugs at around twelve to thirteen years. F. M. Scherer, *The Pharmaceutical Industry — Prices and Progress*, 351 NEW ENG. J. MED. 927 (2004). Biologic drugs, which do not face competition from follow-on products after patent expiration, have substantially longer effective market exclusivity, even before the recent legislation granting twelve years of data exclusivity.

167. GOVERNMENT ACCOUNTABILITY OFFICE, NEW DRUG DEVELOPMENT: SCIENCE, BUSINESS, REGULATORY, AND INTELLECTUAL PROPERTY ISSUES CITED AS HAMPERING DRUG DEVELOPMENT EFFORTS 36 (2006), available at <http://www.gao.gov/new.items/d0749.pdf>.

168. Livermore, *supra* note 140.

169. See Table 1.

170. Kades, *supra* note 19.

occurs when the owner of the intellectual property rights does not bear the cost of increased resistance in the future.¹⁷¹ Some of these theorists suggest that if patents' lengths are increased, it is in the intellectual property owner's financial interest to maintain low resistance rates so that demand for the product does not diminish over time. This is a variant of the patent holder waste hypothesis, known as the "patent holder conservation" hypothesis.¹⁷²

Patent-based initiatives seek to solve the antibiotic crisis by improving the potential revenues of the manufacturers, but it is unclear whether the financial prospects offered will encourage for-profit manufacturers to re-energize their antibiotic development. Using patents as a demand-rationing device is cumbersome, given the existing health care reimbursement systems in the United States.¹⁷³ While companies with existing products will always welcome the financial windfall from a patent extension, the impact on R&D decisions is less clear. The financial incentive offered by longer patents is likely to be quite modest since the additional funds come from exclusive years at the end of the original exclusivity period, which translates to only a small additional net present value.¹⁷⁴ Finally, simply lengthening patent terms does not provide manufacturers with an active incentive to change their behavior and delay profit-making. Since future spending on pharmaceutical products is unpredictable, owners of longer patents may choose to maximize revenues in the short term rather than promote conservation of the antibiotic resource.¹⁷⁵ If there are other manufacturers with antibiotics in the same class, this pressure will be more acute, because bacteria can develop cross-resistance among drugs with similar mechanisms of action.¹⁷⁶

We are also concerned about the ancillary effects of extensions in patents. Such initiatives frequently produce unintended consequences, and in order to achieve socially desirable outcomes, careful attention must be paid to the

171. Otto Cars et al., *Meeting the Challenge of Antibiotic Resistance*, 227 *BMJ* a1438 (2008); Horowitz & Moehring, *supra* note 162; Kades, *supra* note 19; Stephane Mechoulan, *Market Structure and Infectious Diseases*, 40(2) *CAN. J. ECON.* 468 (2005). *But see Longer Antimicrobial Patents*, *supra* note 24.

172. *Legal Ecology of Resistance*, *supra* note 19, at 164-165. Neither hypothesis has been empirically tested thus far.

173. *Vanishing Public Domain*, *supra* note 19; *Legal Ecology of Resistance*, *supra* note 19.

174. *Longer Antimicrobial Patents*, *supra* note 24.

175. *See Longer Antimicrobial Patents*, *supra* note 24; *Vanishing Public Domain*, *supra* note 19. However, some theorists suggest the opposite might occur. Horowitz & Moehring, *supra* note 162; Kades, *supra* note 19.

176. Anna Maria Ferrara, *New Fluoroquinolones in Lower Respiratory Tract Infections and Emerging Patterns of Pneumococcal Resistance*, 33 *INFECTION* 106 (2005). Resistance can develop across different classes, which widens the scope of the coordination problem.

mechanisms employed.¹⁷⁷ For example, there might be global public health implications for antibiotic patent extensions in the United States, because the patent system on pharmaceutical products has been partially globalized through the World Trade Organization's Trade-Related Aspects of Intellectual Property (TRIPs) Agreement and the increasingly complex network of TRIPs plus bilateral and regional trade agreements.¹⁷⁸ Paul Hunt estimates that the globalized patent system has priced two billion people out of the market for patented medicines.¹⁷⁹ If applied to the field of antibiotics, a new product might be less available to patients who need it in low-income settings.¹⁸⁰ In addition to the basic health effects, any modifications to U.S. law would have to account for the difficulties inherent in proposing modifications to the global structure. Many would oppose such changes with respect to low- and middle-income countries given this concern that existing intellectual property laws can hinder access to patented drugs. Purportedly global solutions to resistant infections should also address the needs of these countries, where the majority of infectious disease mortality occurs. ACE incentives can be globalized by simply making the conservation and health impact goals global in focus. This can be achieved in the United States and Europe without regard to the quality of governance institutions in the developing world. The companies have extensive relationships with providers, institutions and governments around the world and would have a

177. For an example of using substantial financial incentives to achieve a socially desirable outcome that is rife with unanticipated consequences, see Aaron S. Kesselheim, *Encouraging Drug Development for Neglected Diseases — The Trouble with FDA Review Vouchers*, 359 *NEW ENG. J. MED.* 1981 (2008).

178. Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, 33 *I.L.M.* 81 (1994), available at http://www.wto.org/english/docs_e/legal_e/27-trips.pdf; Marrakesh Agreement Establishing the World Trade Organization, Apr. 15, 1994, 1867 *UNTS* 154; 33 *ILM* 1144, at Annex 1C, art. 31(b) (1994), available at http://www.wto.org/english/docs_e/legal_e/legal_e.htm; Legal Instruments—Results of the Uruguay Round vol. 31, 33 *I.L.M.* 81 (1994). Prior to the TRIPs Agreement, low-income countries could obtain low-cost copies of medicines under patent in the United States that were produced in places like India and Brazil, where patents on pharmaceutical products were not permitted.

179. See Paul Hunt, *Human Rights Guidelines For Pharmaceutical Companies in Relation to Access to Medicines* (2007) (draft for consultation, on file with authors); see also Oxfam, *Investing For Life: Meeting Poor People's Needs for Access to Medicines Through Responsible Business Practices 2* (Oxfam, Briefing Paper No. 109, 2007).

180. This problem is currently being seen in the case of tenofovir disoproxil fumarate (TDF, or Viread), a newer medication used to treat resistant HIV infections, as countries are facing growing demand but high prices supported by TRIPs-based intellectual property regimes. See, e.g., Tahir Amin et al., *Expert Review of Drug Patent Applications: Improving Health in the Developing World*, 28 *HEALTH AFF.* w948 (2009).

financial incentive to use those levers to achieve the public health goals articulated by ACE.

2. Transferable Intellectual Property Rights

“Transferable intellectual property rights” (TIPRs) have been proposed as an alternative to patent extensions. TIPRs, or “wildcard” patent extensions, would be earned upon development of new antibiotic agents and can be transferred to other drugs to extend their market exclusivity periods.¹⁸¹ In the past, the IDSA has suggested applying them to the field of new antibiotic development.¹⁸² Wildcard patents permit the sponsor to extend market exclusivity for a significant period of time for the most profitable drug in its portfolio, or to sell the right to the highest bidder. Such a market exclusivity extension, if applied to a blockbuster cholesterol-lowering drug such as atorvastatin (Lipitor), whose market exclusivity is due to expire in 2011, could be worth billions of dollars. Advocates of this proposal predicted that if a new antibiotic were developed that fully treated resistant *Pseudomonas aeruginosa*, and if a two-year wildcard patent were applied to a blockbuster drug, the incentive would achieve cost-neutrality within ten years.¹⁸³

There are a number of important public health problems with wildcard patents. The first is cost. Ten wildcard patents have been estimated to cost more than \$40 billion.¹⁸⁴ Even supporters peg the cost of the first wildcard at \$7.7 billion.¹⁸⁵ The opportunity costs of an expenditure of this magnitude must be carefully considered: what other health programs could be underwritten for such a sum? We suggest the ACE program as one alternative.

Second, decoupling of patents from the innovative product is likely to cause hardships for patients taking the drug to which the TIPR is applied.¹⁸⁶ The

181. See Jorn Sonderholm, *Wild-Card Patent Extensions as a Means To Incentivize Research and Development of Antibiotics*, 37 J.L. MED. & ETHICS 240 (2009). But see Kapczynski, *supra* note 40, at 264 (attacking the wild-card proposal).

182. BAD BUGS, *supra* note 9, at 26.

183. See Brad Spellberg et al., *Societal Costs Versus Savings From Wild-Card Patent Extension Legislation To Spur Critically Needed Antibiotic Development*, 35 INFECTION 167 (2007). Notably, this cost estimate assumes that the drug would not have been developed absent the special incentive and ignores the opportunity cost of the proposal.

184. See *Longer Antimicrobial Patents*, *supra* note 24, at 561; see also Kapczynski, *supra* note 40, at 265-66; Kevin Outterson, *Antibiotic Resistance and Antibiotic Development – Author’s Reply*, 8 LANCET INFECTIOUS DISEASES 212-13 (2008).

185. Spellberg et al., *supra* note 183.

186. *Longer Antimicrobial Patents*, *supra* note 24 (“Wildcard patents would operate as a more

emergence of generic drugs and the resulting decrease in cost that occur after patent expiration have been shown to significantly increase access to drugs and adherence by patients to therapeutic regimens.¹⁸⁷ Wildcard patents change this dynamic by delaying expiration of market exclusivity and derive their value by increasing costs on patients and payors of that other product.¹⁸⁸ If applied to an essential drug that helps reduce the risk of recurrent cardiovascular disease, a wildcard patent may end up harming millions—a far greater number of patients than a new drug for a rare multidrug-resistant bacterium may help. If companies are permitted to sell their wildcard patents to other manufacturers, public health authorities are unlikely to scrutinize such transfers, which may include concurrent payments or transfers of other intellectual property rights that can further increase costs or limit access to pharmaceutical products. Since changes in U.S. patent law often have global implications, wildcard patents (and patent length extensions) also may extend the waiting time for patients in resource-poor settings seeking access to the product at marginal cost.¹⁸⁹

Third, the decoupling of patent rewards from the underlying invention is troubling on constitutional and policy grounds. An important potential constitutional objection maintains the novel, plausible claim that the patents clause requires the exclusion right to apply to the underlying invention.¹⁹⁰ On policy grounds, the intimate connection between the exclusion right and the invention are important to the economic efficiency of the mechanism. The market for the invention itself should determine the value of the patent; likewise, patents on inventions with little utility can be disciplined by a low market return. Decoupling the invention from the reward through the TIPRs mechanism thus

than US\$40 billion annual tax on heart disease, hypertension, chronic obstructive pulmonary disease, asthma, and depression to inefficiently cross-subsidize antimicrobial research and development.”).

187. William Shrank et al., *The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions*, 166 ARCHIVES INTERNAL MED. 332 (2006).

188. *Longer Antimicrobial Patents*, *supra* note 24.

189. *Vanishing Public Domain*, *supra* note 19. *See supra* discussion in Subsection III.b.1.

190. A “wildcard” patent that gives an inventor market exclusivity in a different product may not meet the language of the Constitution that permits Congress to provide market exclusivity rights in “their respective . . . discoveries.” *See* U.S. CONST. art. I, § 8, cl. 8. As a counterexample, the pediatric market exclusivity provision applies to drug manufacturers who conduct clinical trials on the use of their products in children and provides six months of additional market exclusivity *to that product*. *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997). This supplementary exclusivity mechanism is directly connected to the invention in a way that is more consistent with the Constitutional language.

unhinges patent exclusions from the key market test of their value, and substitutes an untested administrative process.¹⁹¹ As Amy Kapczynski noted, “wild-card extensions embrace the most difficult aspect of a prize design without offering the benefits that a prize system could provide.”¹⁹² The ACE program will certainly face prize design issues – discussed below – but the payoff is clear because companies are paid only if public health goals are met.

Despite these concerns, a few members of the pharmaceutical industry consider wildcard patents to be the incentive mechanism “most likely to successfully stimulate new antibiotic development.”¹⁹³ Other industry leaders have said privately that they do not support the proposal.¹⁹⁴ Wildcard patents have been considered (and rejected) by Congress as a way of encouraging the creation of countermeasures for bioterrorism agents.¹⁹⁵ At the time of this writing, it appears that the political prospects for applying wildcard patents to the antibiotic market are not great, perhaps in part because their policy and legal obstacles are formidable.

C. Reimbursement Incentives Based on Medical Need

Some proposals to enhance potential revenues for antibiotic drug development work primarily outside the patent system. A fundamental characteristic of market-based reimbursement of patented drugs is that the companies receive revenues based on their ability to sell drugs rather than actual improvement in human health. In countries with insurance coverage for drugs, the market is further disconnected from actual medical need. In countries with strong government health plans, effective healthcare technology assessment can provide better information to the market. For example, in Australia, England, and Germany, coverage for pharmaceuticals is nearly universal and the government exercises significant control over pharmaceutical reimbursement. But if purchaser market power is fragmented for pharmaceuticals (as in the United States) or if the patients are too poor to be salient consumers (as in low-income countries), then the patent-based system can be significantly disconnected from medical need.

Several prominent proposals tie research incentives directly to medical

191. TIPRs are really a variant on the prize proposals discussed in Part C below, but with the prize amount based on the value of another, unrelated patent.

192. Kapczynski, *supra* note 40, at 266.

193. Spellberg et al., *supra* note 183.

194. Interview by Kevin Outterson with anonymous source.

195. Biological, Chemical, and Radiological Weapons Countermeasures Research Act, S. 666, 108th Cong. (2003).

need. James Love and Tim Hubbard have been leaders in delineating prize-based proposals geared to medical need. Love and Hubbard argue that significant prizes can create incentives for engaging in needed research. The public health payoff comes when the ultimate product is dissociated from its development costs and can enter the public domain immediately.¹⁹⁶ As a result, a plan for distribution of the drug can be undertaken without the revenue-related concerns that can prevent dissemination to lower-income settings. These prize fund proposals could provide financial rewards that increase with the estimated social value of the drug, with the largest rewards going to developers of drugs or vaccines for neglected or undertreated diseases.¹⁹⁷ Though still politically novel, and with a number of logistical and theoretical hurdles to overcome, these proposals have gained increased traction in recent years. In 2005, Vermont legislator Bernie Sanders first proposed a bill setting up an \$80 billion prize fund when he was in the U.S. House of Representatives,¹⁹⁸ and he introduced it again in 2007 as a senator.¹⁹⁹ In the 2008 Presidential campaign, candidate John Edwards discussed a prize system alternative to drug patents,²⁰⁰ and in 2008 a proposal for prize funds was submitted by Bolivia and Barbados to the World Health Organization in response to a request by the Intergovernmental Working Group to develop a sustainable global health plan of action for research into essential medicines.²⁰¹ In 2010, the World Health Organization's governing body kept this issue on the table in the ongoing work of an expert working group on research and development.²⁰²

Two other prominent proposals follow similar tracks. Thomas Pogge and Aiden Hollis have proposed a global Health Impact Fund (HIF). The HIF would give companies the option to obtain reimbursement for drugs based on the actual health impact of the drug. The program would be voluntary and contractual, with payments coming from a multi-billion dollar global fund. Payments would be

196. See Love & Hubbard, *supra* note 40. [AU: There are two Love & Hubbards in FN 40. Which one should we cite to?]

197. Joseph E. Stiglitz, *Scrooge and Intellectual Property Rights*, 333 BMJ 1279 (2006).

198. Medical Innovation and Prize Fund Act of 2005, H.R. 417, 109th Cong. (2005).

199. Medical Innovation and Prize Fund Act of 2007, S. 2210, 110th Cong. (2007).

200. James Love, *John Edwards Calls for Prizes To Replace Monopolies as Innovation Incentive for New Drugs*, KNOWLEDGE ECOLOGY INT'L, June 15, 2007, <http://keionline.org/content/view/87/1..>

201. WORKING DOCUMENT PROPOSED BY BARBADOS AND BOLIVIA (2008), available at http://www.keionline.org/misc-docs/b_b_igwg/working_document_barbados_bolivia.pdf.

202. SIXTY-THIRD WORLD HEALTH ASSEMBLY, ESTABLISHMENT OF A CONSULTATIVE EXPERT WORKING GROUP ON RESEARCH AND DEVELOPMENT: FINANCING AND COORDINATION, (2010), available at http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R28-en.pdf.

allocated among the qualifying drugs based on the global health impact of the intervention, as measured statistically in Quality-Adjusted Life Years (QALYs) of the target population.²⁰³ Neglected and undertreated diseases would then have a significant blockbuster market without regard to the wealth or poverty of the patients. Drug companies would also receive financial rewards for marketing to maximize health impact rather than sales. The Health Impact Fund differs from some prize proposals in that it would operate as a complement to the patent system, at the election of the company. As a contract-based legal tool, the Health Impact Fund also falls into Sector 6.²⁰⁴ More controversially, the HIF would allow the sponsor to retain their intellectual property. James Love in particular has been critical of this aspect of the Health Impact Fund, as he claims it would undermine generic markets.²⁰⁵

A third variation on this theme is the Advance Market Commitment (AMC), whereby countries, in concert with international aid organizations, commit to purchase a product meeting certain specifications as a production incentive.²⁰⁶ AMC supporters argue that providing guaranteed demand can help interested manufacturers budget appropriately in the clinical development process, and can encourage companies to pursue promising late-stage products that might otherwise be abandoned for lack of demand.²⁰⁷ In 2007, Canada, Italy, Norway, Russia, the United Kingdom, and the Bill & Melinda Gates Foundation modified this strategy by announcing a \$1.5 billion AMC for vaccines aimed at pneumococcal pneumonia.²⁰⁸ This AMC is less ambitious than the original proposal, since almost all of the research and development work had been completed.²⁰⁹ AMCs are also Sector 6²¹⁰ approaches, but must be negotiated piecemeal, with high transaction costs and the opportunity for process capture by

203. Thomas Pogge, *Human Rights and Global Health: A Research Program*, 36 METAPHILOSOPHY 182 (2005); HOLLIS & POGGE, *supra* note 41; Hollis, *An Efficient Reward System*, *supra* note 41.

204. *See* Table 1.

205. James Love, *Open Licensing vs. Monopoly Controlled Supply*, KNOWLEDGE ECOLOGY INT'L, Apr. 27, 2008, <http://keionline.org/node/88>.

206. MICHAEL KREMER & RACHEL GLENNERSTER, *STRONG MEDICINE: CREATING INCENTIVES FOR PHARMACEUTICAL RESEARCH ON NEGLECTED DISEASES* (2004); Cars et al., *supra* note 171.

207. Ernst R. Berndt et al., *Advance Market Commitments for Vaccines Against Neglected Diseases: Estimating Costs and Effectiveness*, 16 HEALTH ECON. 491 (2006).

208. Theresa Braine, *Controversial Funding Mechanism To Fight Pneumonia*, 86 BULL. WORLD HEALTH ORG. 325 (2008).

209. *Id.*

210. *See* Table 1.

drug companies.²¹¹

All three proposals are readily applicable to the field of antibiotic research, but have limitations that require adjustments. Only the AMC is close to being operational, but the first test is limited to a product nearing the end of development. It has been criticized as resembling little more than a purchase contract for products already launched.²¹² Prize proposals face significant financing and implementation barriers.²¹³ Nevertheless, these proposals may someday shift the current paradigm in global pharmaceutical development, and may be a fruitful area for research and policy articulation. Their application to antibiotics seems especially promising, as any movement towards value-based prizes or reimbursement will dampen company incentives to excessively market antibiotics. The first prong of our ACE program is explicitly an extension of these ideas to antibiotics, by paying prizes or increasing reimbursement to more closely reflect the social need or health impact of the drug. In all three proposals, we would add explicit conditionality, requiring the drug companies to meet antibiotic conservation goals if they are to receive additional funds.

D. Reducing Financial Hurdles for Antibiotic Innovation

Patent modifications and prize-based approaches increase the rewards for innovation. Another strategy is to lower the costs of innovation, through grant support for basic science research (Sector 6) and efforts to reduce regulatory hurdles to successful drug product launches (Sector 4).²¹⁴ If costs are reduced, then perhaps the supply of new drugs can be increased. The Orphan Drug Act is an example of a legal mechanism to reduce costs to the drug sponsor during development, while also increasing potential revenues after marketing.²¹⁵ As in previous work, we support expanded public support for basic antibiotic research,²¹⁶ but here we also raise questions about any expansion of the Orphan Drug Act. We also review safety concerns with efforts to reduce regulatory standards in antibiotic clinical trials.²¹⁷

211. See Light, *supra* note 40.

212. Donald W. Light, *Is G8 Putting Profits Before the World's Poorest Children?*, 370 LANCET 297 (2007).

213. Marlynn Wei, *Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005*, 13 B.U. J. SCI. & TECH. L. 25 (2007).

214. See Table 1.

215. See *infra* Subsection III.D.2.

216. See Kesselheim & Outtersson, *supra* note 25, at 1692.

217. *Id.* at 1692.

1. Enhanced basic science funding

Basic research funding in infectious diseases²¹⁸ can help to better categorize the biology of infectious diseases and the nature of resistance development and can also establish potential targets for antibiotic products. Such scientific investigation into the mechanisms of resistance can lead to more effective conservation programs.²¹⁹ Current investments are remarkably sparse, with the NIH spending about \$200 million per year on antibacterial resistance research.²²⁰ Admittedly, upstream scientific investigation may take time to be developed into viable antibiotic end-products,²²¹ but this way of supporting innovation is still critical, especially given the permanent need for new antibiotic development. Enhanced basic science funding should be an integral complement to any potential programs focused on the downstream drug development process. The funding opportunities provided by the American Recovery and Reinvestment Act of 2009 are welcome steps in the right direction.²²²

218. Though such increased funding could come from any source, the greatest prospect for increased basic research funding comes from public sources. The NIH has maintained a commitment to basic science research over the past few decades, while the pharmaceutical industry has dedicated ever-increasing amounts of its research to later-stage clinical trials. Hamilton Moses III et al., *Financial Anatomy of Biomedical Research*, 294 JAMA 1333 (2005). Notably, the US is currently the worldwide leader in funding of basic science; the US directs about 6% of its total health care spending to biomedical research, far surpassing all other countries in relative and absolute terms. *Id.*

219. Lipsitch & Samore, *supra* note 45.

220. N. Kent Peters et al., *The Research Agenda of the National Institute of Allergy and Infectious Diseases for Antimicrobial Resistance*, 197 J. INFECTIOUS DISEASE 1087 (2008). The modesty of this funding is striking when compared to the cost of the wild-card patent proposal at \$7.7 billion for the first drug: imagine the possibilities if the NIH research budget was quadrupled over the next five years, with sustained funding thereafter.

221. Time from identification of receptors or pathways that can serve as the basis for new antibiotic targets to approval of a new product can take a decade or more. However, there is reason for optimism that this process can be accelerated due to recent developments in translational research, including high-throughput screening. Bernhard A. Müller, *Imatinib and Its Successors – How Modern Chemistry Has Changed Drug Development*, 15 CURRENT PHARMACEUTICAL DESIGN 120 (2009).

222. Gardiner Harris, *Specter, A Fulcrum of the Stimulus Bill, Pulls Off a Coup for Health Money*, N.Y. TIMES, Feb. 13, 2009, at A15, available at <http://www.nytimes.com/2009/02/14/health/policy/14specter.html?em>.

2. Antibiotics under the Orphan Drug Act

Investment can also come in the form of more direct savings to pharmaceutical manufacturers interested in pursuing antibiotics. For example, the Orphan Drug Act (ODA) template includes tax incentives and research grants, both of which decrease the cost to the pharmaceutical company of up-front investment in research and development.²²³ The ODA could be considered a form of federal cost-sharing for qualifying research projects. Under this legislation, however, the pharmaceutical manufacturer retains full control of the profits of any end product developed with the use of these government funds. In these cases, patients are arguably paying twice for drugs: first through the public funds supporting development of the innovative products, and second through the high prices that orphan drugs command from patients and public payors.²²⁴ An

223. The actual cost of drug development is a widely debated figure. Most pharmaceutical industry sources refer to figures from DiMasi, Grabowski, and others, that suggest that the estimate exceeds \$800 million in 2004 dollars. See Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003). Other consultants for the pharmaceutical industry report the value is as high as \$1.7 billion for a “blockbuster” drug. See Ashish Singh et al., *Healthy Convergence*, IN VIVO (2004), http://www.bainlab.com/bainweb/publications/publications_detail.asp?id=17177&menu_url=publications_results.asp. But these figures are likely overestimates, particularly for drugs developed with initial investment from public research funding. These values have been criticized for including the cost of capital in their research estimates. See Arnold S. Relman & Marcia Angell, *America's Other Drug Problem*, 16 NEW REPUBLIC 27 (2002). Other estimates have suggested the real cost of new drug development averages closer to \$240 million. See RUTH RUTTENBERG & ASSOCIATES, INC., NOT TOO COSTLY, AFTER ALL: AN EXAMINATION OF THE INFLATED COST ESTIMATES OF HEALTH, SAFETY, AND ENVIRONMENTAL PROTECTIONS (2004), available at <http://www.citizen.org/documents/ACF187.pdf>. Still, these remain high figures, with substantial risk involved. Whatever the value, reducing unnecessary costs in drug development remains a worthy goal. See Michael Rawlins, *Cutting the Cost of Drug Development?*, 3 NATURE REVIEWS DRUG DISCOVERY 360 (2004).

224. See MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT (Random House 2004); see also Diana Porter, AARP Policy Brief, Pharmaceutical Companies Maintain Huge Profits with High-Priced Pills (2003), available at http://www.retiredamericans.org/docs/G1/profpills_issuebrief_final.pdf. This point is a subject of substantial debate, of course. See Frank R. Lichtenberg, *Are the Benefits of Newer Drugs Worth Their Cost? Evidence from the 1996 MEPS*, 20 HEALTH AFF. 241 (2001). But see Yuting Zhang & Stephen B. Soumerai, *Do Newer Prescription Drugs Pay for Themselves? A Reassessment of the Evidence*, 26 HEALTH AFF. 880 (2007). Most opponents of this view argue that manufacturer input is integral to the drug development process. We do not disagree with this point; however, we believe that the role of government-funded basic research is not fully accounted for in these estimates.

alternative system would seek better public returns on such investment in corporate research, either through limitations on prices from drugs arising from publicly funded research or a requirement that the ultimate manufacturer contribute a share of its revenues on these products to the basic science research commons.²²⁵ In the ACE program, the conditionality is unrelated to prices or revenues, but linked to public health goals.

The FDA Amendments Act of 2007 set aside financial support for a conference intended to identify whether the incentives contained in the ODA might be extended to certain antibiotics developed to treat “serious and life-threatening infectious diseases, such as diseases due to gram-negative bacteria and other diseases due to antibiotic-resistant bacteria.”²²⁶ Other groups have made similar recommendations.²²⁷ The ODA was passed in 1983 to encourage research focused on therapeutic agents for the treatment of rare conditions, for which a limited patient pool could otherwise prevent recovery of the investment made in product development.²²⁸ It is usually applied to diseases that affect less than two hundred thousand people in the United States, although companies can apply for diseases affecting more than two hundred thousand if they can establish that developing a drug for the condition is uneconomic because there is “no reasonable expectation” that U.S. sales could support development of the drug.²²⁹ The ODA provides manufacturers with three primary incentives: 1) federal funding of some grants and contracts to perform clinical trials of orphan products; 2) a research tax credit of 50% of clinical testing costs; and 3) an exclusive right to market the orphan drug for seven years from the date of marketing approval. Through 2010, over three hundred and fifty products with orphan designations have received marketing authorization in the United States.²³⁰

225. Kesselheim & Avorn, *supra* note 82.

226. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 1112, 121 Stat. 823, 976 (2007).

227. Spellberg et al., *supra* note 183.

228. For a history of the Orphan Drug Act, see Henry A. Waxman, *The History and Development of the Orphan Drug Act*, in ORPHAN DISEASES AND ORPHAN DRUGS 135-45 (I. Herbert Scheinberg & J.M. Walshe eds. 1986).

229. 21 U.S.C. § 360ee(b)(2) (2006). Manufacturers rarely use this option because it involves displaying their financial projections and business strategy to regulators and others who might seek to obtain the information through a Freedom of Information Act request.

230. FOOD AND DRUG ADMINISTRATION, LIST OF ORPHAN DESIGNATIONS AND APPROVALS (2010), available at <http://www.fda.gov/orphan/designat/list.htm>; M. Miles Braun et al., *Emergence of Orphan Drugs in the United States: A Quantitative Assessment of the First 25 Years*, 9 NATURE REVIEWS: DRUG DISCOVERY 519, 519-22 (2010).

Some commentators suggest “extending the Orphan Drug Act to antibiotics,”²³¹ but the Act already applies to emerging products in this market. While the greatest number of orphan products treats cancer, many target infectious diseases caused by viral and bacterial pathogens.²³² 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.”²³³ The designation was achieved without new legislation.²³⁴

Thus, the emphasis on the ODA is curious, and it is unclear how modifying it for antibiotics might be implemented. It should not be necessary to loosen the ODA’s population limits for antibiotics because the two-hundred-thousand-U.S.-person limit is not an absolute barrier. As described above, companies can gain orphan designation for larger groups if they can establish economic necessity. Empirical evidence suggests that this limit has not been a factor in marketing approvals under the ODA generally.²³⁵ The campaign to apply the ODA to antibiotics appears to ignore the history of FDA approvals under the Act.

We also caution against any plan that calls for antibiotic orphan drugs to receive longer than the ODA-designated seven-year exclusivity term. The ODA has been hailed for promoting drug development for rare conditions,²³⁶ but to our knowledge no studies have demonstrated its overall cost-effectiveness.²³⁷ Some designated orphan drugs are used for broader purposes, which belies the rhetoric of orphan drugs. For example, the anemia drug epoetin alfa (Epoen) was originally approved in 1989 as an orphan product for anemia associated with end-stage renal disease, but it has been used for many other indications, such as

231. A. Bruce Montgomery, *Reply to the Antibiotics Pipeline—Challenges, Costs, and Value*, 351 NEW ENG. J. MED. 2019, 2019-20 (2004).

232. Braun et al., *supra* note 230.

233. *Id.*

234. Critics may note that the designated drug (levofloxacin) is not new, but this is hardly a warrant for the extension of the ODA. Many of the approved designations under the ODA are for new uses of existing products. For example, in March 2004, Merck received an orphan drug designation for rofecoxib (Vioxx) for “[t]reatment of juvenile rheumatoid arthritis.” *Id.*

235. See Braun et al., *supra* note 230 (“The most common patient population size for orphan designations and approvals was fewer than 10,000 patients . . .”).

236. Marlene E. Haffner, *Adopting Orphan Drugs—Two Dozen Years of Treating Rare Diseases*, 354 NEW ENG. J. MED. 445, 445-47 (2006).

237. David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L. J. 125, 125-43 (2000).

cancer-related anemia, as well as in patients with mildly low red blood cell counts but without symptoms of anemia.²³⁸ The manufacturer's annual revenue for Epogen grew to \$1.4 billion by 1996 and continues as a blockbuster more than a decade later,²³⁹ with sales exceeding \$2.4 billion in 2008.²⁴⁰ Many other products originally protected by the orphan designation are used off-label and provide substantial returns for their sponsor, which calls into question the necessity of the ODA in these circumstances.²⁴¹ One logical counterargument is that these off-label uses cannot be predicted at the time of drug development, but this misunderstands the relationship between the ODA and drug marketing. Qualifying for ODA status does not commit a company to apply for any particular label, but they will receive the additional incentives only for the specific ODA uses. With new drugs with sufficient patent life remaining, the ODA gives companies an incentive to apply for a narrow use affecting less than two hundred thousand patients per year to obtain the tax credits and grants. When finally approved by the FDA, the company can sell the drug to a much wider group, whether on- or off-label. Facing patent expiry in a few years, companies can take existing popular drugs and look for narrower clinical indications as a new orphan use. The primary goal for these drugs is the additional seven years of market exclusivity, which blocks generic entry even if the patent is expired. This latter group would also include drugs for which the patents have expired: the additional seven years of marketing exclusivity will block sales of rival generic drugs for that use, despite the absence of a valid patent.

Rather than implementing an expansion of orphan market exclusivity for antibiotics, we recommend a thorough and independent review of the cost-effectiveness of the ODA, including an evaluation of possible limits on the current ODA exclusivity term that ends when a new product is used for additional indications and becomes more profitable than anticipated. In particular, any modification of the ODA for antibiotics should be supported by careful empirical evidence of cost-effectiveness of the intervention, including

238. Surrey M. Walton et al., *Prioritizing Future Research on Off-Label Prescribing: Results of a Quantitative Evaluation*, 28 PHARMACOTHERAPY 1443, 1450 (2008).

239. Geeta Anand, *How Drugs for Rare Diseases Became Lifeline for Companies*, WALL ST. J., Nov. 15, 2004, at A1.

240. Press Release, Amgen, Amgen's Fourth Quarter 2008 Adjusted Earnings Per Share Increased 6 Percent to \$1.06; Full Year 2008 Adjusted Earnings Per Share Increased 6 Percent to \$4.55 (2009), available at http://www.amgen.com/media/media_pr_detail.jsp?year=2009&releaseID=1248352.

241. This is particularly true of oncology-related drugs. See Paolo G. Casali on behalf of the Executive Committee of ESMO, *The Off-Label Use of Drugs in Oncology: A Position Paper by the European Society for Medical Oncology (ESMO)*, 18 ANNALS ONCOLOGY 1923 (2007).

opportunity costs. More fundamentally, an expansion of the ODA to include antibiotics targeting more than two hundred thousand people directly conflicts with conservation goals. The ACE program is designed to be a more carefully designed response to the unique needs of the antibiotic market.

3. Reducing the costs of regulation

Before new pharmaceutical products can be legally sold, they must pass approval by the relevant drug regulatory agency. However, representatives of the pharmaceutical industry have attributed the decline in new product development in part to the overly rigorous evaluative process required by the FDA, locating this proposal in Sector 4.²⁴² For most drugs, the FDA allows placebo-controlled trials to support drug approval.²⁴³ However, ethics rules would forbid the use of placebos in people with serious infections.²⁴⁴ These studies utilize an active control, generally an approved antibiotic. Such trials are most frequently organized to demonstrate that the experimental antibiotic is not significantly inferior to the standard treatment; the relevant difference is referred to as the

242. See Martin L. Katz et al., *Where Have All the Antibiotic Patents Gone?*, 24 NATURE BIOTECHNOLOGY 1529 (2006); see also Alexander T. Tabarrok, *Assessing the FDA via the Anomaly of Off-Label Prescribing*, 5 IND. REV. 25 (2000). This argument was the intellectual underpinning for the *Abigail Alliance v. Von Eschenbach* case, involving a claim that there was a constitutional right for terminally ill patients to access unapproved prescription drugs. Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The Case of Abigail Alliance v. Von Eschenbach*, 297 JAMA 205 (2007). The argument found initial support in a three-member panel in the District of Columbia Court of Appeals before being overturned in an en banc hearing. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006), *rev'd en banc*, 495 F.3d 695 (D.C. Cir. 2007).

243. The placebo-controlled trial is generally considered to be the gold standard for proving efficacy in clinical trials, but it can have numerous flaws. The FDA has long considered two pivotal placebo-controlled trials as serving as a reasonable basis for a drug approval decision. Alan Davies & Peter D. Stonier, *Development of Medicines: Full Development*, in TEXTBOOK OF PHARMACEUTICAL MEDICINE 310, 310-31 (5th ed. 2006). It has been criticized because the placebo can be an improper comparator that does not provide any useful information about a drug as compared to other therapies for a particular disease. Jerry Avorn, *FDA Standards — Good Enough for Government Work?*, 353 NEW ENG. J. MED. 969, 970 (2005).

244. Robert J. Temple, *When Are Clinical Trials of a Given Agent vs. Placebo No Longer Appropriate or Feasible?*, 18 CONTROLLED CLINICAL TRIALS 613 (1997). Once treatment for a disease has progressed usefully, then it may no longer be reasonable to randomly assign someone in need of therapy to a placebo arm. David Knopman et al., *Clinical Research Designs for Emerging Treatments for Alzheimer Disease: Moving Beyond Placebo-Controlled Trials*, 55 ARCHIVES OF NEUROLOGY 1425 (1998).

“delta.”²⁴⁵ A non-inferiority trial design can be controversial depending on the level of the delta required by regulators to prove the drug’s utility.²⁴⁶ Demonstrating non-inferiority with a low delta in a comparison with an active control means that more patients must be included in a Phase III study of an antibiotic to show a statistically significant difference.²⁴⁷ Studies with large numbers of patients are more expensive to conduct.

Regulatory requirements directly relate to clinical trial costs, which are among the largest investments in drug development.²⁴⁸ As a result, some commentators have suggested that lower regulatory hurdles may encourage for-profit pharmaceutical manufacturers to return to the field of antibiotics.²⁴⁹ Such a move would both decrease the direct costs in premarketing studies and increase the expected returns from longer effective market exclusivity due to shorter regulatory preparation and review times. Norrby and colleagues recommend placing a greater emphasis on studies showing the properties of the drug and allowing extrapolations from data generated in one type of infection to others.²⁵⁰ Baquero and colleagues suggest awarding limited marketing authorization based on earlier Phase II studies and beginning the Phase III studies while the

245. Larry L. Laster & Mary F. Johnson, *Non-Inferiority Trials: The ‘At Least as Good as’ Criterion*, 22 STAT. MED. 187 (2003). The non-inferiority trial, as with other facets of clinical trials, has been the subject of much investigation intended to make it more efficient for drug developers in the antibiotic field. Kem F. Phillips, *A New Test of Non-Inferiority for Anti-Infective Trials*, 22 STAT. MED. 201 (2003). For a recent review by the GAO, see GOVERNMENT ACCOUNTABILITY OFFICE, *supra* note 104, at 1-32 (discussing issues with non-inferiority trials for antibiotics).

246. Norrby et al., *supra* note 68. Recently, pharmaceutical manufacturers have expressed concern that the FDA is tightening the delta and clinical even further by tightening the statistical parameters. David M. Shlaes & Robert C. Moellering Jr., *The United States Food and Drug Administration and the End of Antibiotics*, 34 CLINICAL INFECTIOUS DISEASES 420 (2002).

247. Mark Rothmann et al., *Design and Analysis of Non-Inferiority Mortality Trials in Oncology*, 22 STAT. MED. 239 (2003).

248. Clinical trial costs are currently the largest driver of drug development costs. According to Moses et al., *supra* note 218, “the proportion of total pharmaceutical research and development expenditures (including those outside the United States) that has gone to clinical trials (phases 1-3) has increased from 28% in 1994 to 41% in 2003. In addition, the proportion of research and development funds that has supported phase 4 trials has increased from 5% in 1994 to 11% in 2003.” One response from many pharmaceutical manufacturers is to move more clinical trials overseas to countries where patients can be accrued for lower costs. Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816 (2009).

249. See Shlaes & Moellering, *supra* note 246.

250. *Id.*

antibacterial agent is already available for use.²⁵¹ Livermore contends that historical controls can provide effective comparisons and proposes that approval be extended to related indications (such as infections or types of microbes) based on microbiological data, rather than additional human trials.²⁵²

Despite these proposals for adjustments to the regulatory process, the effects of such adjustments are far from clear. Approved antibiotics usually have short mean and median clinical development times, as compared to other drug classes.²⁵³ In the United States, the FDA already has programs to speed its regulatory evaluation of important new antibiotics. First, the “fast track” program begins early in the clinical trial process.²⁵⁴ It is designed to facilitate the development of a New Drug Application (NDA) and expedite the review of drugs to treat serious diseases that fill an unmet medical need.²⁵⁵ Second, novel antibiotics aimed at multidrug resistant pathogens would also certainly qualify for the FDA “priority review” program, under which the FDA completes its regulatory review within six months after full NDA submission.²⁵⁶ For example, the antibiotic tigecycline (Tygecil), the first glycylicline, received the benefit of both the fast track and the priority review systems.²⁵⁷ The FDA has also taken a number of steps in the last few years to streamline the regulatory process for approval of antibiotics, including publishing guidelines to help manufacturers design trials with less uncertainty about FDA expectations, allowing smaller sample sizes for individual studies, and actively working with sponsors during the early development phase.²⁵⁸

251. Fernando Baquero et al., *Antibiotic Clinical Trials Revisited*, 46 J. ANTIMICROBIAL CHEMOTHERAPY 651 (2000).

252. Livermore, *supra* note 140.

253. Joseph A. DiMasi, *Success Rates for New Drugs Entering Clinical Testing in the United States*, 58 CLINICAL PHARMACOLOGY THERAPIES 1 (1995); Janice M. Reichert, *Trends in Development and Approval Times for New Therapeutics in the United States*, 2 NATURE REVIEWS DRUG DISCOVERY 695 (2003).

254. Janice M. Reichert et al., *A Decade of the Fast Track Programme*, 7 NATURE REVIEWS DRUG DISCOVERY 885 (2008).

255. Food and Drug Administration Modernization Act of 1997, *supra* note 190.

256. SUSAN THAUL, CRS REPORT FOR CONGRESS: FDA FAST TRACK AND PRIORITY REVIEW PROGRAMS(2008), available at <http://www.nationalaglawcenter.org/assets/crs/RS22814.pdf>.

257. FOOD AND DRUG ADMINISTRATION, NME DRUG AND NEW BIOLOGIC APPROVALS IN 2005 (2009), available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NMEDrugandNewBiologicApprovals/ucm081676.htm>.

258. John H. Powers, *Antimicrobial Drug Development—The Past, the Present, and the Future*, 10 CLINICAL MICROBIOLOGY & INFECTION (Supp. 4) 23 (2004).

There are also important disadvantages to loosening regulatory requirements. Premarketing drug trials can help determine the efficacy of a product, but are often underpowered to detect important adverse effects.²⁵⁹ Such adverse effects only arise after the drug has been approved. However, in a number of recent cases, overly aggressive drug promotion has led many people to receive unnecessary prescriptions for dangerous prescription drug products that were later withdrawn from the market.²⁶⁰ The chance that an important safety concern with a product will be missed in pre-approval testing rises as regulatory requirements are lowered.²⁶¹ There may also be risks to speedy regulatory review. Carpenter and colleagues recently showed that approvals of new drugs by the FDA made in the two months before a regulatory deadline were associated with more subsequent safety problems, suggesting negative consequences to imposing such deadlines on FDA drug review.²⁶² Any proposal to loosen regulatory requirements, then, must be considered with a critical eye and with an appropriate view of the potential safety risks.²⁶³ Several of the recently approved antibiotics have demonstrated some important safety issues after marketing approval by the FDA.²⁶⁴ In fact, more than half of all antibiotics approved by the U.S. FDA in the two decades following 1980 were subsequently removed from the market, although not all explicitly for safety-related concerns.²⁶⁵

259. The “power” of a trial is related to the number of patients enrolled. For example, randomized controlled trials are designed with the appropriate power to test the primary outcome. If a randomized controlled trial is powered to test a primary efficacy endpoint, not enough patients may be enrolled to demonstrate adequately whether other secondary outcomes, such as safety-related endpoints, are reached. Bruce M. Psaty, *Clinical Trial Design and Selected Drug Safety Issues for Antibiotics Used To Treat Community-Acquired Pneumonia*, 47 *CLINICAL INFECTIOUS DISEASE* (Supp. 3) S176, S177-78 (2008).

260. Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 *JAMA* 308, 308 (2007).

261. For example, orphan drugs are nearly all approved on an accelerated basis in small numbers of patients. While such parameters may be reasonable for orphan drugs, because the diseases these drugs treat are only found in small populations of patients, there are clinical implications for permitting accelerated approval based on testing in fewer numbers of patients (both proxies for less stringent pre-marketing regulatory requirements). An early government-led analysis suggested that 31% of orphan drugs on the market had demonstrated more pronounced side effects during pre-approval clinical testing than non-orphan drugs, and following FDA approval, 13% produced more side effects than anticipated. See Susan F. Scharf, *Orphan Drugs: The Question of Product Liability*, 10 *AM. J. LAW & MED.* 491, 504-05 (1989).

262. See generally Carpenter et al., *supra* note 158.

263. See Outterson et al., *supra* note 104.

264. See Outterson et al., *supra* note 67.

265. *Id.* Notably, this risk of subsequent removal from the market presents another limitation

Drug safety is a significant concern, which argues against weakening the antibiotic approval process. For some of the most essential antibiotics, it may be worth taking on these additional risks. At the same time, systems such as active post-marketing surveillance should be in place to assure that a product's safety is being actively monitored.²⁶⁶ Provisional approval of antibiotics for a few years under close post-marketing surveillance is a possible compromise position that dovetails nicely with the ACE incentives described below. More broadly, the ACE program takes the financial pressure off companies seeking a speedy and possibly premature approval of an antibiotic. Under ACE, the companies will also have an incentive to act on their private knowledge of safety and efficacy issues for the benefit of public health.

E. Conclusion

The proposals that have been offered to address antibiotic drug development are limited by concerns related to their implementation (see Table 2). None of these alternatives sufficiently addresses the underlying trouble with the antibiotic market: that conservation and innovation incentives might negatively interact. In the next section, we describe in detail the ACE incentives, a panel of market changes that can help bring these incentives in better alignment.

to prize funds that reward development of new products upon their approval. Our ACE proposal accounts for the possibility of needing supplemental prizes, but the primary rewards are incremental, as certain public health outcomes are met. Thus, a drug that is later withdrawn for safety reasons would not waste ACE incentive resources.

266. Wendy Brewster et al., *Evolving Paradigms in Pharmacovigilance*, 1 CURRENT DRUG SAFETY 127 (2006).

TABLE 2: SUMMARY OF CURRENT POLICY PROPOSALS TO ADDRESS RISING ANTIBIOTIC RESISTANCE

Policy category	Strategy	Examples	Benefits	Concerns
Conservation	Infection control	Isolation beds, hand-washing, “search and destroy” programs	Most direct tool to limit infection and resistance	May slow but not stop resistance, limited funding, reduces drug company revenues
	Rational antibiotic use	Academic detailing, clinical treatment guidelines, formulary restrictions, prior authorization requirements	Addresses antibiotic misuse, some very successful implementation	Programs are often hospital-specific rather than system-wide, limited funding, reduces drug company revenues
Property-based incentives	Patent length extension	Start patent at regulatory approval, extend patent term to more than twenty years	Financial costs are indirect, valuable to some drug companies	High costs for patented drugs, non-transparent, rewards the wrong companies, may damage conservation
	Transferable Intellectual Property Rights (TIPRs)	Proposals range from six months to two years	Valuable to large pharmaceutical companies, financial costs are indirect	Transfers costs to other fields, non-transparent, may damage conservation
Value-based reimbursement	Prizes	Global prize funds, Health Impact Fund, Advance Market Commitments (AMC)	Rewards selected based on public health gains. In some proposals, drug enters public domain	Barriers to implementation and financing, questions about AMC capture by industry

Reducing drug development costs	Enhanced funding for basic science	National Institutes of Health, private foundations	Develops basic tools and human capital which can lead to new antibiotics and better conservation	No substantial concerns, though funding may take time to achieve results
	Specific development programs	Orphan Drug Act (ODA)	ODA has been credited with producing numerous drugs for rare diseases	Already applies to antibiotic field, cost-effectiveness not known, does not support conservation
	Alters the regulatory review process	Loosen FDA standards, accelerate review time, allow access to drugs before completion of regulatory review	Reduce clinical trial costs, a potential barrier to antibiotic investment	Safety concerns, accelerated resistance from early marketing of new antibiotics

IV. THE ANTIBIOTIC CONSERVATION AND EFFECTIVENESS (ACE) PROGRAM

The essential concept of the ACE program is to rationalize private incentives more closely to the ultimate public health goals. Our favored legal tool in the ACE program is contract: deploying insurance reimbursement, prizes, and grants for both conservation (Sector 5) and production incentives (Sector 6).²⁶⁷ We articulate the primary objective to be continued antibiotic effectiveness, which requires a balanced pursuit of both conservation and new production. A significant question is which institutions to target with ACE incentives. Ideally, the target would be able to internalize all of the negative costs from antibiotic misuse and the positive benefits from antibiotic conservation. The target should also have ready access to private information about antibiotic use. As we describe below, the drug companies appear to be best positioned to successfully integrate the disparate economic incentives in this field. The companies can act directly to induce conservation and can also influence others (such as doctors and

267. See Table 1.

hospitals) to follow suit.

The ACE program emphasizes: (1) value-based reimbursement of antibiotics from public payors such as Medicare and Medicaid, with spillover participation from private payors (Sectors 5 and 6). These reimbursement changes will improve private markets for antibiotic effectiveness by giving significant institutional actors financial incentives to promote conservation and continued antibiotic effectiveness: (2) making these payments conditional on meeting realistic public health and conservation goals, including a Strategic Antibiotic Reserve (Sectors 5 and 6),²⁶⁸ (3) regulatory changes, including limited waivers of antitrust and self-dealing laws, to permit market coordination for conservation (supporting efforts in multiple Sectors), and (4) increased public grant support for basic antibiotic research, including both conservation and new production (Sectors 5 and 6).²⁶⁹ In this section, we discuss the details of these proposals in further depth and show how ACE incentives can be instituted without wholesale changes to the current drug approval, patent, and market exclusivity systems.

A. Value-Based Reimbursement of Antibiotics

The first plank of the ACE program is value-based reimbursement²⁷⁰ for antibiotics.²⁷¹ The market undervalues antibiotics. The gross sales of antibiotics in the United States in 2008 were approximately \$11.2 billion.²⁷² Expressed as a percentage of the U.S. pharmaceutical market,²⁷³ antibiotics represent about 3.9% of United States drug sales. Given that low percentage, it is understandable that antibiotics accounted for about 3.6% of all U.S. drug approvals since 2000.²⁷⁴ Antibiotic innovation is delivering about the number of new drugs that its market size suggests. The market places a modest private value on this important class of

268. See Table 1.

269. See Table 1.

270. This reimbursement could take many forms, including increased ex-manufacturer pricing or prizes awarded under contract. If reimbursement mechanisms were chosen, care would have to be taken to isolate patients and perhaps plan sponsors from the increased costs, perhaps through a reverse rebate directly from the government to the patent holder. If the goal were to minimize changes to insurance reimbursement systems, then a prize system is preferred. Prizes have the disadvantage of requiring separate financing, while reimbursement is built into the health care insurance system.

271. Kesselheim & Outterson, *supra* note 25, at 1692.

272. IMS Midas Database (2008 USD_MFN) (\$11,195,825,230) (manufacturers' sales prices).

273. IMS Health, Top Therapeutic Classes by U.S. Sales (Apr. 6, 2010), http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%2520Therapy%2520Classes%2520by%2520U.S.Sales.pdf.

274. See Outterson et al., *supra* note 67.

drugs and companies respond appropriately. With present spending patterns, antibiotics are not in the top fifteen global therapeutic drug classes, ranked by market size.²⁷⁵ To demonstrate that the market undervalues antibiotics, we must compare the private value with some other referent. One possibility is the social burden of infectious disease in high-income countries. We calculate this value from the World Health Organization estimates of the disability-adjusted life year (DALY) burden of infectious diseases in various WHO regions. To translate DALYs to dollars, we provide a range of assumptions on the social value of a DALY, assuming that an additional healthy year of life is worth from \$50,000 to \$125,000 each. Table 3 (below) presents the results, suggesting that the unmet social burden of infectious disease in the United States and Canada is worth \$73-\$183 billion per year. Providing \$10 billion per year in ACE incentives would still be a terrific bargain for society if it reduced these DALYs by an even greater amount.

TABLE 3: UNMET SOCIAL BURDEN OF INFECTIOUS DISEASE IN SELECTED HIGH-INCOME COUNTRIES²⁷⁶

Assumed DALY Value (in '000s)	\$50	\$75	\$100	\$125
Social cost (US/CAN) (in billions of USD)	\$73.3	\$110	\$146.7	\$183.3
Social cost (High Income Europe) (in billions of USD)	\$66.3	\$99.5	\$132.6	\$165.8
Total social cost (US/CAN & High-Income Europe) (in billions of USD)	\$139.6	\$209.5	\$279.3	\$349.5

275. IMS Health, Top 15 Global Therapeutic Classes, 2009, Total Audited Markets, *available at* http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Top%2015%20Global%20Therapeutic%20Classes_2009.pdf.

276. Underlying burden of disease data from WHO 2008. Estimates by Outterson (2009). These estimates do not include the social value of averted infectious diseases in high-income countries. The cost of resistant infections is a much smaller subset, reaching approximately \$30 billion per year in the United States.

A second possible referent is the social value of the current health impact of antibiotics. The calculations in Table 3 are limited to the current unmet health need and do not include the current health impact delivered by today's antibiotic treatments. Life in a post-antibiotic world would be remarkably more dangerous, with profound impacts on human health. If ACE incentives were able to merely preserve the current level of antibiotic effectiveness, this success would be worth tens of billions of dollars, if not more. The estimates in Table 3 might be far too low, underestimating the true social value of antibiotics.

In short, the market as it currently operates places an inappropriately low private value on antibiotics and infection control.²⁷⁷ The reimbursement price for both should more closely track their social value. But the U.S. health care markets have many dysfunctional aspects; thus some therapies receive too much reimbursement,²⁷⁸ while others receive too little.²⁷⁹ Antibiotics have historically been priced relatively cheaply. Whatever the precise cause, a process for refashioning this system must begin with modeling the health impact of new antibiotics and pricing accordingly. For example, if a new drug led to a reduction in length of hospital stay for patients with a certain kind of bacterial pneumonia, a value-based reimbursement plan will return a percentage of these savings to the company. When used in conjunction with the conservation-based exclusivity discussed below,²⁸⁰ the company's immediate financial success will be conditioned on the continued effectiveness of the drug. Conversely, as resistance builds on a drug, ACE payments will automatically taper. This approach begins to remedy the mismatch between social value and private value, which we identify as a central problem in antibiotic markets. Make no mistake: we are proposing a very substantial increase in payments for antibiotics, driven by the social value of these important drugs. The total monetary value of ACE incentives might be a net increase of several billion dollars a year in the United States, even as unit sales decline. In fact, declining unit sales would be an expected result as antibiotic conservation techniques received full stakeholder support with financial incentives. Reimbursement for the value provided by infection control and antibiotic stewardship activities undertaken by providers and public health authorities should similarly increase.

Expert groups from a myriad of disciplines have suggested that drugs be

277. Matthew E. Falagas et al., *A Comparative Study of the Cost of New Antibiotics and Drugs of Other Therapeutic Categories*, PLoS ONE e11 (2006).

278. Deborah Schrag, *The Price Tag On Progress—Chemotherapy For Colorectal Cancer*, 351 NEW ENG. J. MED. 317 (2004).

279. Robert A. Steinberg, *Easing the Shortage in Adult Primary Care—Is It All About Money?*, 360 NEW ENG. J. MED. 2696 (2009).

280. See *infra* notes 275-287

reimbursed in accordance with their value to society.²⁸¹ In the United States, the American Recovery and Reinvestment Act created a federal agency to organize comparative effectiveness studies.²⁸² The process of modeling the health impact of antibiotics and rating their utility is a logical task for such a body to undertake, with assistance from experts at Medicare and others familiar with large patient databases. The U.S. pharmaceutical industry has been critical of comparative effectiveness research, expecting that total reimbursements will decline and thus undermine innovation incentives.²⁸³ In the specific case of antibiotics, we think these concerns are misplaced, as the purpose of the ACE program is to increase the private value of these drugs to more closely mirror social value.

B. Conditioning Reimbursement on Meeting Conservation Targets

The second leg of the ACE incentive program links these enhanced financial rewards to appropriate use and successful conservation of the antibiotic. In addition to higher prices to the manufacturer (but not the patient), cash prizes can be used as incentives. The key concept here is conditionality, making the enhanced payments only if conservation goals are met at a population level.

Insurance reimbursement and cash prizes are favored over patent extensions and additional marketing exclusivity²⁸⁴ because they operate directly and immediately with less discounting to present value. Insurance reimbursement and cash prizes significantly change the cash flow stream in all years and substantially alter the net present value of conservation management by the antibiotic sponsor. Unlike traditional R&D pull incentives, the time lag between company action and financial reward could be quite short with ACE reimbursement and prizes.²⁸⁵ By contrast, patent modifications may be more

281. See, e.g., OFFICE OF FAIR TRADING, THE PHARMACEUTICAL PRICE REGULATION SCHEME (2007), available at http://www.offt.gov.uk/shared_offt/reports/comp_policy/oft885.pdf; HOLLIS & POGGE, *supra* note 41; Hollis, *supra* note 41; Love & Hubbard, *The Big Idea*, *supra* note 40, at 1519; Joseph E. Stiglitz, *Scrooge and Intellectual Property Rights*, 333 *BMJ* 1279 (2006).

282. Jerry Avorn, *Debate About Funding Comparative-Effectiveness Research*, 360 *NEW ENG. J. MED.* 1927 (2009).

283. See, e.g., John A. Vernon, Joseph H. Golec & Steadman Stevens, *Comparative Effectiveness Research (CER) and the Potential Threat to Pharmaceutical Innovation* (2010), available at <http://ssrn.com/abstract=1579442>.

284. Our proposal does not rely on patent-term extensions, but rather on FDA-administered periods of marketing exclusivity while conservation targets continue to be met, coupled with greatly improved reimbursement or cash prizes after regulatory approval of the antibiotic. *Fighting Antibiotic Resistance*, *supra* note 25.

285. Unlike patent term extension proposals, which must influence company R&D behavior years before actual cash flow, ACE incentives can provide immediate cash flow for meeting

uncertain from a company's view since they provide projected rewards, discounted to net present value, and only if future sales materialize. In addition to being a weaker production incentive, patent modifications do not give strong incentives for conservation.

Unlike other regulatory exclusivity proposals,²⁸⁶ the ACE program would condition payment to the continued effectiveness of the antibiotic. The sponsor can thus forecast a return on investment from managing antibiotic effectiveness for the long term. This incentive is likely to be much more cost-effective than patent modifications, because the amount of the additional incentive will be conditioned on meeting public health goals. Patents do not employ this condition. ACE incentives could also be tailored to individual drug-bug pairings and various levels of resistance, in order to prevent the antibiotic sponsor from losing financial rewards all at once. For a drug treating MRSA, for example, one target could be working to ensure that morbidity from MRSA in a representative sample of U.S. healthcare institutions remains below a set percentage.²⁸⁷ This proposal would give the drug companies stronger financial incentives to promote conservation tools in hospitals and otherwise manage antibiotics for population-level public health.

ACE relies on drug companies to rationalize this market characterized by asymmetrical information and irrational economic incentives. Focusing ACE incentives at the pharmaceutical company allows the company to internalize and address the dynamic cross-purposes that characterize existing battles between conservation and new production. One objection is that the company does not fully control the utilization of antibiotics, making ACE incentives a partially effective policy lever. We concede that drug companies cannot achieve conservation alone, but we see value in co-opting these companies to the cause of public health. The companies control the patents, possess significant private information on antibiotic markets, and control significant resources to influence prescription patterns. No other private actor can claim so much. There is

conservation targets. If the time lag between company actions and significant resistance is quite long, then a time-lag discounting problem may also arise for ACE, necessitating a range of measures such as unit sales in addition to pathogen susceptibility.

286. *See, e.g.*, Roin, *supra* note 89.

287. These targets could be designed by a roundtable of experts led by government, but also including representatives from academia, non-profit research groups, and industry. Sensible organizations to lead this target-setting group include the FDA, Centers for Medicare and Medicaid Services (CMS), and the Centers for Disease Control. Models for this type of cooperation and medical evaluation abound at the government level. One example is the Medicare Evidence Development and Coverage Advisory Committee, which provides independent guidance and expert advice to CMS on specific clinical topics.

substantial empirical evidence that pharmaceutical manufacturers actively direct drug product use through marketing. Pharmaceutical manufacturers devote over \$50 billion dollars per year to promotional and advertising practices in the U.S. pharmaceutical market alone.²⁸⁸ These efforts include direct physician contact through sales representatives, advertising to consumers and physicians via the media, lay press, and industry publications, provision of free samples of products, distribution of consulting fees or other payments that may act as inducements to prescribers, and development of sponsored Continuing Medical Education conferences touting the benefits of their product that are required of physicians by state medical licensing boards. Studies have shown the impact that these tactics can have on physician prescribing behaviors.²⁸⁹ Promotional and advertising practices can lead physicians to prescribe more expensive, though less effective, drug products against expert recommendations.²⁹⁰ This effect has been shown to be especially prevalent among prescribers of antibiotics.²⁹¹

Currently, private financial incentives reward companies for promoting the sales of their antibiotics. As a result, pharmaceutical marketing efforts are exclusively directed towards increasing prescriptions of the company's antibiotic. Companies can increase the sales of their antibiotic in two primary ways: (1) increase the overall sales of antibiotics (grow the market); or (2) shift demand to their drug from a rival drug (increase market share). Growing the market produces positive externalities for other antibiotic manufacturers, as the benefits from a growing market may spill over to rival producers. Growing the market also produces unclear health effects. If the additional use is not clinically rational, growing the market creates negative public health externalities through resistance. Antibiotic conservation directly threatens the market growth model.

The second strategy entails several different characteristics. Increasing market share is positive for the company (additional sales, with fixed costs spread over a larger revenue base) and directly negative to rivals, who lose sales in a zero-sum game. Shifting market share from one drug to another may also have unclear health effects. If the better drug gains more market share, health should be positively impacted. The opposite is also possible: a company may convince physicians to prescribe and patients to take a less effective drug. Market shifts with negative public health externalities are perhaps more likely when the

288. Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLOS MED. e1 (2008).

289. Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is A Gift Ever Just a Gift?*, 283 JAMA 373 (2000).

290. Avorn, *supra* note 161.

291. John D. Cleary, *Impact of Pharmaceutical Sales Representatives on Physician Antibiotic Prescribing*, 8 J. PHARMACY TECH. 27 (1992).

older, more effective drug is generic and lacks a company champion with a large marketing budget to defend market share. Many of these questions are empirical, and the companies themselves control much of the relevant data. We emphasize that rational policy making in drug innovation will be difficult without either the cooperation of the companies or careful empirical analysis of the data they control. Under the ACE program, the companies will have significant financial incentives to use their private information and marketing resources for the benefit of public health goals.

The companies may also be formidable opponents to new conservation programs. In recent years, a number of pharmaceutical manufacturers have been cited for aggressive over-promotion of their drugs.²⁹² The efforts to encourage rational prescribing and develop evidence-based prescription guidelines have been limited because the investment in these public health efforts has been dwarfed by the pharmaceutical industry's investment in marketing, which is not necessarily aligned with public health goals. Under the ACE program, pharmaceutical industry promotional practices (such as physician detailing by pharmaceutical sales representatives and Continuing Medical Education) would be refocused for a purpose more in line with public health needs. The ACE incentives would encourage drug companies to target clinically rational use of their products in patients where the drugs would reduce morbidity, while at the same time encouraging the sponsor to restrict resistance-inducing overuse of the product. Industry promotional practices would also be incentivized to encourage efforts aimed at promoting rational prescribing practices and infection control. For example, manufacturers might consider cooperating with hospitals in restricting formularies, rather than seeking agreements or other mechanisms to undermine the practice.²⁹³ The pharmaceutical industry marketing departments possess remarkable tools to influence physician prescribing practices. Under the ACE program, they would be turned into a mechanism for helping encourage proper use, not overuse, of new antibiotic agents. The government selects the public health goals, then the companies privately manage the process to achieve those goals.

Other levels of the market could be considered for ACE incentives, such as the physician, the hospital, or the patient.²⁹⁴ By choosing the company, we

292. Aaron S. Kesselheim & David M. Studdert, *Whistleblower-Initiated Enforcement Actions Against Health Care Fraud and Abuse in the United States, 1996-2005*, 149 ANNALS INTERNAL MEDICINE 342 (2008).

293. See Robert Pear, *U.S. Warns Drug Makers on Illegal Sales Practices*, N.Y. TIMES, Apr. 28, 2003, available at <http://query.nytimes.com/gst/fullpage.html?res=9D0CE2DB133DF93BA15757C0A9659C8B63>.

294. See, e.g., Saver, *supra* note 32 (focusing on the physician).

deliver the incentive to the most powerful upstream player in the system, which then can deploy portions of that prize downstream, as they deem most effective.²⁹⁵ A drug company receiving a \$100 million ACE incentive might find it cost effective to offer grants to hospitals with particular infection control problems, to the extent that such an effort helps the company continue to meet its ACE goals. Giving conservation incentives merely to doctors and hospitals, for example, pits them against the pharmaceutical marketing machine and fails to tap into the companies' vast market knowledge.²⁹⁶

D. Limited Waivers of Antitrust and Self-Dealing Laws

Our final proposal addresses horizontal and vertical coordination problems in antibiotic markets. The biology of resistance does not respect the lines drawn by patents or antitrust law. Antibiotic resistance can cross multiple species and diminish the effectiveness of antibiotics both within classes and across classes. Resistance patterns are heterogeneous, which complicates conservation efforts.²⁹⁷ Some private antibiotic conservation strategies would function better if manufacturers could cooperate horizontally in limiting the marketing, sale, and utilization of antibiotics with cross-resistance issues. For example, only two firms currently hold patents on commercially significant FDA-approved drugs in the fluoroquinolone class of antibiotics,²⁹⁸ but resistance to these drugs can easily affect other drugs in this class.²⁹⁹ The class itself should be understood as a form of commons, at least with respect to resistance. If the number of players was too large or transaction costs too high, perhaps regulation would be appropriate. The other option is private group coordination, which could be effective in this case given the relatively small number of sophisticated actors. If fluoroquinolones are to be managed for long-term public health, all of the relevant patent holders must work together to jointly manage the market. The patent owners (pharmaceutical

295. These payments may require exemptions from fraud and abuse laws and antitrust laws. See discussion *infra* Section IV.C.

296. ACE does not require the companies to disclose their private market information. The companies manage their actions as they see fit, in order to obtain the ACE incentives.

297. See *Vanishing Public Domain*, *supra* note 19, at 96-97.

298. Ortho-McNeil (levofloxacin and ofloxacin) and Bayer (ciprofloxacin and moxifloxacin). BMS withdrew gatifloxacin from the US market in April 2006 following publication of a negative article in the *New England Journal of Medicine* and Pfizer's US sales of alatrofloxacin ceased in 2003.

299. G. Thomas Ray et al., *Hospital-Level Rates of Fluoroquinolone Use and the Risk of Hospital-Acquired Infection with Ciprofloxacin-Nonsusceptible Pseudomonas Aeruginosa*, 41 CLINICAL INFECTIOUS DISEASE 441 (2005).

companies) must work together to conserve antibiotics.

Competition law appears to forbid exactly this form of joint coordination among competitors. The pharmaceutical industry has received significant attention from competition authorities with regard to its patent and litigation settlement practices.³⁰⁰ In this circumstance, however, economic models of drug resistance suggest “a mixed competition/monopoly regime can perform better than competition or monopoly alone.”³⁰¹ Likewise, hospitals and payors in a community might improve the public health by coordinating conservation activities on specific pathogens across all hospitals and payors, but might be reticent to do so given the possible sanction of antitrust laws. There are indications that authorities could be favorably disposed to such coordination. The U.S. Federal Trade Commission and Department of Justice have issued joint guidelines suggesting health care joint ventures that would otherwise be anticompetitive might be permitted in narrow circumstances.³⁰² Proper circumstances include clinical coordination to improve quality, which is the goal of antibiotic conservation.

Therefore, our third ACE proposal creates limited conservation-based antitrust waivers. We propose that the FDA identify particular bug-drug pairings for which cross-resistance is a problem. The IDSA has clearly identified pathogens of special concern in the United States because limited therapeutic options remain. These pairings might be an appropriate starting point. The FDA would be empowered to issue certificates, in consultation with the antitrust enforcement agencies that would permit limited joint coordination of conservation activities for the specified product markets. The concept we are proposing is akin to structure of the safe harbor exceptions to the Anti-Kickback statute, which lists a number of activities that are systematically excluded from federal prosecution.³⁰³ In this case, the certificates would signal to private actors that joint coordination for antibiotic conservation was clearly encouraged, while limiting the potential for collusive mischief by specifying the qualifying drug-bug combinations. In this vein, we also support extending marketing exclusivity to the companies, again conditioned on meeting conservation targets. So long as

300. BUREAU OF COMPETITION, AGREEMENTS FILED WITH THE FEDERAL TRADE COMMISSION UNDER THE MEDICARE PRESCRIPTION DRUG, IMPROVEMENT, AND MODERNIZATION ACT OF 2003: SUMMARY OF AGREEMENTS FILED IN FY 2007 (2008), *available at* <http://www.ftc.gov/os/2008/05/mmaact.pdf>.

301. Mechoulan, *supra* note 171, at 4.

302. U.S. DEP'T OF JUSTICE AND FED. TRADE COMM'N, STATEMENTS OF ANTITRUST ENFORCEMENT POLICY IN HEALTH CARE (1996), *available at* <http://www.justice.gov/atr/public/guidelines/0000.htm>.

303. 42 U.S.C. §§ 1320a-1327b(b)(3) (2006).

firms are successfully managing the resource for long-term public health, they should be allowed to continue without the threat of generic entry in the antibiotic market. Generic entry adds another actor to the group that must coordinate activities, complicating efforts. If a company fails to meet the conservation goals, it might be appropriate to place the exclusive marketing rights into the hands of the government or another firm better poised to manage the resource.

Limited antitrust waivers will create a forum for possibly collusive discussions well beyond these particular antibiotics. Perhaps the meetings should be public, to facilitate coordination amongst the downstream actors as well. In any event, the industry does not lack other opportunities for market discussions, and if collusion occurs in other drug markets it can hardly be blamed on the ACE program.

In addition to this horizontal coordination problem, drug companies will also want to incentivize their downstream stakeholders to cooperate in their antibiotic conservation efforts. As a result, we predict that drug companies will more readily support vertical antibiotic conservation efforts in hospitals and physician offices, because the success of these programs will most directly determine the extent of antibiotic resistance development—and continued revenue generation for the sponsor. Likewise, hospitals and independent long-term care facilities share patient populations that could benefit from a coordinated effort against resistance.³⁰⁴ The self-dealing laws, including Stark II, prohibit many forms of financial relationship amongst referral sources.³⁰⁵ It may be necessary to create specific safe harbors and exceptions to permit vertical coordination of antibiotic conservation efforts.

V. IMPLEMENTATION ISSUES WITH ACE INCENTIVES

A. Designing Value-Based Reimbursement

ACE incentives need not be uniform. A powerful new antibiotic should receive a greater reward; me-too antibiotics with minimal value and doubtful safety profiles should perhaps receive nothing at all, or even be penalized. ACE incentives should respond to the health impact of the drug. This will be a difficult task, with many technical obstacles and the ever-present threat of industry capture. Any pay-for-performance or value-based reimbursement system shares these risks. We address them only briefly here.

Building on the work of the IDSA task force, teams of infectious disease

304. See Outterson, *supra* note 18.

305. Joan H. Krause, *A Conceptual Model of Health Care Fraud Enforcement*, 12 J.L. & POL'Y 55 (2003).

specialists, in consultation with government and international public health experts, should establish targets for ACE incentives that consist of microbes with emerging resistance to current therapy and/or substantial public health impact. Expert groups should then attempt to identify the size of the potential market and health impact for the needed antibiotic in each case by working with government officials, representatives from the pharmaceutical or biotech industries, and health economists. Factors related to the disease target, such as its morbidity, effectiveness of current treatment strategies, and rate of emerging resistance, can be used to identify the upper and lower bounds of the public health goals and therefore the ACE incentive. Development-related factors, such as the ease of pharmacological research and rapidity of natural selection at the level of microbe, will affect the costs of development and pretrial testing.

The population health goals for any new agent should be flexible, taking into account the dynamics of the health care system as well as the characteristics of the target microbe. A new agent against VRE may find a much easier implementation strategy in acute care settings in developed countries, where VRE is most prevalent. Using this strategy will require additional investment in improved surveillance of antibiotic use and development of resistance. At timely intervals, the same infectious disease experts and public health officials who set the ACE incentive targets will judge the success of the product in treating the infectious disease for which it was approved.

Value-based reimbursement will also need to consider the structure of licensing agreements in the industry, which typically pay royalties based on sales during the patent term. ACE incentives should be considered sales for these purposes, at least as a default rule. For many antibiotics, the company marketing the product did not invent the molecule but acquired it through a license agreement from an inventor based at a university, non-profit research center (such as an academic medical center), or university-affiliated start-up biotechnology company. Some of the payments under ACE may not be included in the royalty calculations under some license agreements, which would be a windfall to marketer and a loss to the original innovator. The companies will have to amend their licenses, or perhaps a default rule could be integrated into the structure of the ACE contract itself.

Finally, it should be noted that since the private value of antibiotics is such a small fraction of the social value, the amount of the value-based reimbursement system does not have to be finely tuned at first. As described above, the social value of antibiotics appears to be an order of magnitude higher than their private value. So long as clinically important conservation targets are set and the amount of ACE incentives are in the range of several billion dollars per year, we can expect that the resulting expenses will be well spent. The program may well be cost-effective within the health insurance sector alone, without even considering

broader positive externalities.

B. The Strategic Antibiotic Reserve

Limited periods of exclusivity, combined with value-based reimbursement, may not provide a reasonable potential market for some clinically important antibiotics. For example, a first-in-class antibiotic might need to be held in reserve for many years, and used only in the most urgent cases. We call this concept the Strategic Antibiotic Reserve (SAR).³⁰⁶ The clinical value of the SAR has already been demonstrated with the natural history of vancomycin, a drug that was inadvertently held in reserve for decades and is now a major antibiotic in helping manage MRSA and other extremely potent microbes.³⁰⁷

Holding a first-in-class antibiotic in reserve might be the right answer for public health, but it will be a financial disaster for the company, especially if the unit sales are quite small. It will be difficult for value-based reimbursement to deliver hundreds of millions of dollars in annual sales for several years of very sparing use. If the social value of holding a new class of antibiotic in the SAR is, to assume an example, \$200 million per year, it seems unwieldy to charge \$1 million each to two hundred patients (or to their insurers). Neither will longer periods of marketing exclusivity help much, since drugs in the SAR are by definition used only in extreme need and therefore the future projected sales revenue will be deeply discounted. The net present value of additional years of exclusivity after the patent term may be quite small.

For this reason, the ACE program includes supplemental cash prizes for placing important new antibiotics in the Strategic Antibiotic Reserve. These amounts must be quite substantial in order to properly align incentives, ranging towards a billion dollars per year for an important drug class. Current candidates might include daptomycin, a recent antibiotic with activity against MRSA. An expert advisory committee should make the designation of which antibiotics are worth reserving in this way. The financial arrangement with the company will be entirely voluntary, based on a contract with the government. The amount of the payment should be value-based as described above to promote both innovation and conservation. If a company tried to hold out with a critically important antibiotic, of course the government would retain the ability to use a compulsory license, with payment of just compensation for the taking.³⁰⁸

306. See *Legal Ecology of Resistance*, *supra* note 19, at 624, 656-57, 677.

307. See *Legal Ecology of Resistance*, *supra* note 19, at 656.

C. Other Considerations

1. Intellectual Property

The ACE program does not replace the current patent-based exclusivity regime. Antibiotic patents are left in the hands of the companies. One exception to retaining patent rights might be the Strategic Antibiotic Reserve. For these drugs, an alternative model might be a voluntary government purchase of the patent for fair market value.³⁰⁹ A patent buyout would eliminate the company's uncertainty as to the future value of the patent by setting a mutually agreed price. However, we see advantages to keeping the patent in the hands of the companies, even for a drug in the Strategic Antibiotic Reserve. A key goal of the ACE incentives is to co-opt the companies by giving them a continuing financial incentive to develop and sell antibiotics in line with public health needs. If a patent buyout severs that ongoing financial risk/reward to the company, then that incentive is lost. This is especially troublesome in the case where a company then markets follow-on drugs in the same functional resistance group, because the use of these drugs would reduce the strategic value of the previously-purchased antibiotic.

It should be noted that we are limiting this discussion to antibiotics. Generic access to cheap antibiotics is not entirely positive for public health, even on a merely static basis. Cheap (or free) antibiotics drive resistance and reinforce the overall low reimbursement levels in this drug class.³¹⁰ For other classes of antimicrobials, a different balance might be struck between patent law and generic access. Consider antiretrovirals (ARVs) used to treat AIDS. The reimbursed price for first-line treatment in the United States is very high, over \$10,000 per year, while the generic price in aid programs in sub-Saharan Africa is less than \$100.³¹¹ This huge pricing differential was a keystone is ramping up

308. See, e.g., JEROME H. REICHMANN WITH CATHERINE HASENZAHN, NON-VOLUNTARY LICENSING OF PATENTED INVENTIONS (2003), available at http://ictsd.org/downloads/2008/06/cs_reichman_hasenzahl.pdf.

309. See, e.g., Kevin Outterson & Aaron S. Kesselheim, *Market-Based Licensing for HPV Vaccines in Developing Countries*, 27 HEALTH AFF. 130, 134-35 (2008) (discussing a patent buyout for HPV vaccines).

310. See *supra* note 38 and accompanying text.

311. Outterson, *supra* note 154.

treatment for millions of impoverished AIDS patients.³¹² This model was triggered by unlicensed generics produced by Indian generic companies. For these ARVs, public health demanded quicker access to generics.

We have formulated the ACE program as voluntary, based in contract. New drug sponsors will have a choice of whether to enroll their patent-protected antibiotic in the ACE program. A voluntary system may be more palatable to pharmaceutical manufacturers because it is a less extreme step and gives them a veto. However, a voluntary arrangement is complicated by a number of logistical issues that might undermine the effectiveness of the ACE program. First, it would be difficult to incentivize adherence to ACE guidelines if a manufacturer were to refuse to participate and marketed their drug in a way that damaged other antibiotics through resistance. It might be necessary to control a rogue manufacturer through FDA restrictions on the sale and use of their product. Second, it would be complicated to manage the ACE system if it were to include some new antibiotics but not others. For example, the system may experience administrative difficulties if it attempted to limit value-based reimbursement to only selected antibiotics. It might be difficult to specify causal relationships in cross-drug resistance within and between classes. Similarly, limited waivers of antitrust law may be more difficult to manage if the owners of some antibiotics in a particular class were outside the regulatory framework. Most of these problems will wane as more companies participate and also as we develop better understandings of the underlying biological relationships in resistance through public investment in basic research.

These issues may not be a realistic problem if the value-based reimbursement system was quite robust and generous. Hopefully, the companies will be eager to see increases in the reimbursement level for this class of drugs. Alternatively, the government also retains the power of eminent domain, with the condition of paying just compensation.³¹³ Governments also have monopoly power as a purchaser. This is effectively the current market situation in countries where government payors dominate the pharmaceutical market, including the European Union, Canada, and Australia.³¹⁴ Even in the United States, the role of government payors looms larger after the recent expansions in Medicare Part D

312. See Charles B. Holmes et al., *Use of Generic Antiretroviral Agents and Cost Savings in PEPFAR Treatment Programs*, 304 JAMA 313 (2010).

313. See Aaron S. Kesselheim & Jerry Avorn, *Biomedical Patents and the Public's Health: Is There a Role For Eminent Domain?*, 295 JAMA 434 (2006).

314. U.S. DEP'T OF COMMERCE, INT'L TRADE ADMIN., PHARMACEUTICAL PRICE CONTROLS IN OECD COUNTRIES: IMPLICATIONS FOR U.S. CONSUMERS, PRICING, RESEARCH AND DEVELOPMENT, AND INNOVATION 59, 77, 105 (2004), available at <http://www.ita.doc.gov/td/chemicals/drugpricingstudy.pdf>.

and Medicaid.³¹⁵

2. Access to Generic Antibiotics

Under ACE, prices to the patient will not change. From a health plan and social perspective, an expensive but effective antibiotic that meets a public health need is preferable to a low cost but ineffective one, particularly in a country with an adequate social insurance scheme for drugs. We recognize the significant impact of high drug prices in low- and middle-income countries, which calls for full exploitation of TRIPs flexibilities and differential pricing to equitably balance access needs.³¹⁶ It may not be necessary to affect the pricing in developing countries at all. The entire cost of the ACE program can and should be borne by high-income countries.

As to the developing countries, if an impact on global antimicrobial resistance is desired, then the ACE conditions should include both domestic and international targets. Of course, if the companies are being asked to manage a larger problem, their financial incentives must be increased appropriately. But this company mechanism benefits from not being directly dependant on the quality of governance in the developing world. The companies are adept at getting things done despite weak governance structures. They could put that knowledge to work against global antibiotic resistance.

3. Public Investment in Antibiotic Research

Part of the ACE program involves enhanced investment in basic science funding that may lead to new antibiotic development. There have been numerous occasions where important drugs have emerged primarily as a result of public sector investment. For example, in the case of the anti-cancer drug paclitaxel, the NIH invested \$484 million to fund research that eventually allowed Bristol Myers-Squibb to secure FDA approval for this compound. Bristol Myers-Squibb

315. Kevin Outterson & Aaron Kesselheim, *How Medicare Could Get Better Prices on Prescription Drugs*, 28 HEALTH AFF. 832, w832-41 (2009).

316. Kevin Outterson, *Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets*, 5 YALE J. HEALTH POL'Y L. & ETHICS 193 (2005). The TRIPS Agreement is a global floor of minimum intellectual property rights. TRIPS flexibilities are non-mandatory legal tools available to WTO Members to enable each country to balance the twin goals of innovation and access to medicines. Differential pricing in this context is the willingness of drug companies to modify prices based on the ability of the purchaser to pay. Wealthy purchasers pay more; low-income populations pay much less.

marketed the drug as Taxol, earning \$9 billion in worldwide profits.³¹⁷ As a result, we anticipate that improved public funding of infectious disease and resistance research will ultimately develop useful end-products, or discoveries that lead directly to the development of new antibiotics. In cases where new antibiotics are developed in part from public funding, it may be appropriate to adjust the value-based reimbursement level to reward the end-product manufacturer at a level commensurate to the amount of investment it has made in the development of the product. If the drug was developed solely with private funds, then perhaps the value-based reimbursement should allow the company to capture the greater part of the social surplus from the drug. For drugs with significant public support, the proportion would be lower.³¹⁸ As a result, a larger percentage of the health care savings brought by the antibiotic would inure back to the government to help account for its investment drug development. This feedback mechanism supports government investment in the next generation of innovative drugs.

One objection is that this model might discourage private acceptance of public grant funding, since the large pharmaceutical companies would want to avoid the conditions described above. We think this is unlikely. Most recipients of NIH grant moneys are universities and other non-profit research groups. These groups depend on grant funding in a direct, immediate sense and will not oppose an explicit license term that modifies potential royalties to account for public support.

4. Cross-Boundary Antibiotic Management Issues

The ACE program will need to account for the ability of microorganisms to spread resistance features across political and social boundaries. For example, overuse of antibiotics also occurs outside the realm of human medicine. Livestock farmers use antibiotics to increase production efficiency, which can

317. U.S. GEN. ACCOUNTING OFFICE, TECHNOLOGY TRANSFER: NIH-PRIVATE SECTOR PARTNERSHIP IN THE DEVELOPMENT OF TAXOL (2003), available at <http://www.gao.gov/new.items/d03829.pdf>.

318. Notably, there is a risk that manufacturers would use public funds for their research and then refuse to participate in voluntary ACE contracts. In fact, many highly transformative drugs have been based on extensive public funding and then distributed via private markets at high cost to consumers. See Bhaven N. Sampat, *Academic Patents and Access to Medicines in Developing Countries*, 99 AM. J. PUB. HEALTH 9 (2009). However, if the ACE program sufficiently alters the reimbursement scheme for antibiotics to provide manufacturers with a competitive rate of return for new products that are properly managed, we predict that this problem will be minimized.

enhance profitability and also lower food prices for consumers.³¹⁹ While antibiotics in livestock feed can help to promote animal growth, it has been linked to rising resistance rates in both animals and humans.³²⁰ In 2008, the FDA issued an order banning the extra-label use of cephalosporin antibiotics in animal feed out of concern for rising resistance rates.³²¹ European authorities have moved more quickly to restrict animal uses of antibiotic classes that are important to human health.³²² These animal uses currently serve as a source of profits to antibiotic manufacturers. However, under the ACE program, manufacturers of new antibiotic agents will be better incentivized to take resistance emerging from cross-species uses into account when considering how to optimize use of their agents, which should make such additional regulations less necessary. Low-value uses in the animal sector will be replaced by higher-value uses in humans because the ACE incentives are conditioned on meeting public health goals.

Another important cross-boundary issue in the implementation of the ACE program involves whether a national-level response is the correct one. In a globalized world, perhaps all resistance issues are global. The medical evidence is more complex, as usual. To an unexpected degree, resistance issues can be local. In the Netherlands, extensive programs at the national level have maintained resistance at quite low levels.³²³ In nearby France, Italy and Greece, utilization and resistance are much higher.³²⁴ The Netherlands maintains this gradient across an open political barrier, which speaks to the power of national

319. Gay Y. Miller et al., *Productivity and Economic Impacts of Antibiotics Used for Growth Promotion in US Pork Production*, 35 J. AGRIC. & APPLIED ECON. 469 (2003).

320. Frank M. Aarestrup et al., *Glycopeptide Susceptibility Among Danish Enterococcus Faecium and Enterococcus Faecalis Isolates of Animal and Human Origin and PCR Identification of Genes Within the VanA Cluster*, 40 ANTIMICROBIAL AGENTS CHEMOTHERAPY 1938 (1996); Anthony E. van den Bogaard et al., *High Prevalence of Colonization with Vancomycin- and Pristinamycin-Resistant Enterococci in Healthy Humans and Pigs in the Netherlands: Is the Addition of Antibiotics to Animal Feeds To Blame?*, 40 J. ANTIMICROBIAL CHEMOTHERAPY 454 (1997); H. Gregg Claycamp & Barry H. Hooberman, *Risk Assessment of Streptogramin Resistance in Enterococcus Faecium Attributable to the Use of Streptogramins in Animals; Virginiamycin Risk Assessment (2004)* (draft for comment, available at <http://www.fda.gov/downloads/AnimalVeterinary/NewEvents/CVMUpdates/UCM054722/pdf>).

321. 73 Fed. Reg. 38,110 (Jul. 3, 2008).

322. Press Release, President of the Court of First Instance, *The President of the Court of First Instance Rules that Economic Interests Cannot Outweigh the Need To Protect Public Health* (June 30, 1999), available at <http://curia.europa.eu/en/actu/communiqués/cp99/cp9948en.htm>.

323. Wertheim et al., *supra* note 148.

324. H. Goossens, *Antibiotic Consumption and Link to Resistance*, 15 CLINICAL MICROBIOLOGY & INFECTION 12, 13 (2009).

regulatory and cultural institutions to shape resistance patterns in the hospital and the community. So while we concede that many resistance issues might be global, we also insist that many national efforts such as this one are not in vain. A successful implementation of ACE in the United States could prompt similar efforts in the European Union and other valuable pharmaceutical markets. As the largest pharmaceutical market, the changes we propose to the United States will have significant spillover effects in the world, both in the types of new antibiotics that are developed and in the effectiveness and commitment to conservation globally. Since most pharmaceutical company profits are derived from U.S. sales, the ACE program will change the marketing of antibiotics globally. Inappropriate overuse in non-U.S. settings may contribute to resistance development, so pharmaceutical manufacturers will be incentivized by the ACE program to appropriately encourage conservation of their products elsewhere. Given the fact that large pharmaceutical manufacturers commonly use promotional activities to drive prescribing practices in non-U.S. markets,³²⁵ we predict that their contributions can help stem antibiotic resistance arising from lower-income settings. If the value-based reimbursement is sufficiently generous, companies will manage the resources globally even in the absence of parallel efforts in other major markets.

The ACE program can also be adapted to global needs. As discussed above, the U.S. government's infectious disease advisers could keep global public health goals in mind when setting the conditions for ACE participation. Additional prizes could be contemplated for meeting global conservation targets. But these coordination tasks are complex, and the information on cross-resistance and the mobility of resistance may be difficult to interpret. We support the work of the traditional public health agencies of governments in this effort, but also suggest that the ACE program brings the companies on board as partners in these efforts. If the companies enjoy some informational advantages in these markets, their enthusiastic cooperation may be essential to continued global effectiveness of these drugs. ACE allows the companies to use this private information for public health, without requiring public disclosure.

CONCLUSION

We share the concern that current incentives for antibiotic development are inadequate, but insist that new models are required before the market can properly evolve. Public health goals and the goals of the private actors—primarily pharmaceutical manufacturers—are woefully misaligned. Therefore,

325. JOEL LEXCHIN, *DECEPTION BY DESIGN: PHARMACEUTICAL PROMOTION IN THE THIRD WORLD* (1995).

we promote value-based reimbursement that includes grants and prizes supporting both the production and conservation of antibiotics in an integrated program that accounts for dynamic effects and maximizes benefits to society. The ACE incentives, which are grounded less in property and more in contract, will address many of the problems that promote antibiotic resistance, especially the mismatch between the private value and social value of antibiotics. The incentives are focused on the private actors best positioned to coordinate private information and internalize both positive and negative externalities from antibiotic use. Most importantly, all payments are conditioned on continuing to meet conservation goals. Together, this package improves antibiotic markets for long term sustainability, a task that is urgently needed to avoid the disaster of a post-antibiotic era.