

PHARMACEUTICAL POLICY IN THE UNITED STATES IN 2019: AN OVERVIEW OF THE LANDSCAPE AND AVENUES FOR IMPROVEMENT

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INTRODUCTION

Pharmaceutical policy is a source of perennial public debate in the United States. Prescription medication use is ubiquitous and has a significant impact on the health of individual patients as well as populations. The United States spends about \$450 billion each year on prescription drugs, with additional tens of billions of taxpayer and private dollars sunk into discovery and testing of new drugs. Currently, many key pharmaceutical therapies for chronic diseases such as high blood pressure and depression can be obtained for \$4 per month, or less, due to a vibrant generic drug marketplace in the United States.¹ There have been great advances in the use of prescription medications for treating heart disease and certain types of cancer, but there has also been limited progress in treating other conditions, such as Alzheimer's disease² and tropical infectious diseases.³ High prescription drug prices threaten to limit availability of new transformative medications like the treatments for hepatitis C virus infection,⁴ as well as decades-old products like insulin⁵ and antibiotics.⁶

Often at the center of the discussion about how the U.S. pharmaceutical marketplace could function more effectively and efficiently is the Food and Drug Administration (FDA) and the various laws and regulations that play an integral role in patient access to treatment. In the past few years, there have been numerous efforts discussed to reform or modernize aspects of the FDA's function and the legal framework impacting drug development and use. For example, Congress passed the 21st Century Cures Act of 2016 to accelerate

1. See Patrick Liu et al., *Medicare Beneficiary Out-of-Pocket Costs for Generic Cardiovascular Medications Available Through \$4 Generic Drug Discount Programs*, 169 ANNALS INTERNAL MED. 817, 817 (2018).

2. See Roy Anderson et al., *Why Do So Many Clinical Trials of Therapies for Alzheimer's Disease Fail?*, 390 LANCET 2327, 2327 (2017).

3. Nina Jain et al., *Association of the Priority Review Voucher with Neglected Tropical Disease Drug and Vaccine Development*, 318 J. AM. MED. ASS'N 388, 388 (2017).

4. Brandy Henry, *Drug Pricing & Challenges to Hepatitis C Treatment Access*, 14 J. HEALTH & BIOMEDICAL L. 265, 269 (2018).

5. Jing Luo et al., *Strategies to Improve the Affordability of Insulin in the USA*, 5 LANCET DIABETES & ENDOCRINOLOGY 158, 158 (2017).

6. Jonathan D. Alpern et al., *Trends in Pricing and Generic Competition Within the Oral Antibiotic Drug Market in the United States*, 65 CLINICAL INFECTIOUS DISEASES 1848, 1848 (2017).

discovery, development, and delivery of new treatments for patients,⁷ and the sixth reauthorization of the Prescription Drug User Fee Act (FDA Reauthorization Act of 2017).⁸ User fees paid by the pharmaceutical industry now provide about 45% of the FDA's budget,⁹ and the sunset of user fees every five years has provided an impetus for regular amendments to the drug regulatory landscape.

To help understand the key features of the current U.S. pharmaceutical policy landscape, as well as the factors contributing to market function (or malfunction), we reviewed its three major time periods: (1) innovation and related issues (pre-FDA approval); (2) FDA evaluation and review; and (3) post-market safety surveillance (post-FDA approval). We evaluated how different U.S. laws and regulations affect each aspect of this landscape to determine how policymakers could optimize development, approval, and use of prescription medications. The drug development process can be a long and arduous path, beginning with discoveries in synthetic or medicinal chemistry and ending with the FDA's approval of a drug to treat a specified condition.¹⁰ We will proceed chronologically, discussing regulatory issues, highlighting important research studies and evaluating pharmaceutical policy proposals in the context of such studies. We will highlight aspects of the legal and regulatory regime that the data show are functioning well—such as most parts of the generic drug market—and those that are functioning poorly, such as the way brand-name drug prices are set.

I. INNOVATION

A. Sources of Drug Discovery

The road to FDA approval of a new drug begins with seminal basic science discoveries that may provide greater understanding of disease or a new potential target for therapy.¹¹ Product-by-product analyses repeatedly find that academic institutions and non-profit organizations are the source of much of

7. See 21st Century Cures Act of 2016, Pub. L. No. 114-255; see also A.S. Kesselheim & Jerry Avorn, *New "21st Century Cures" Legislation: Speed and Ease vs Science*, 317 J. AM. MED. ASS'N 581, 581 (2017).

8. Food and Drug Agency Reauthorization Act, Pub. L. No. 115-52 (2017); Jonathan J. Dartow et al., *Speed, Safety, and Industry Funding: From PDUFA I to PDUFA VI*, 377 NEW ENG. J. MED. 2278, 2278 (2017).

9. FDA, FACT SHEET: FDA AT A GLANCE 2 (2019), <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm553038.htm>.

10. CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE 1-22, (Bernard Lo & Marilyn J. Field eds., Inst. of Med. 2009).

11. Richard C. Mohs & Nigel H. Greig, *Drug Discovery and Development: Role of Basic Biological Research*, 3 ALZHEIMER'S DEMENTIA 651, 651 (2017).

this fundamental work.¹² The Federal Government, through the National Institutes of Health (NIH), foundations, and internal institutional sources, fund more than 75% of such key research.¹³ Translational research then adapts these basic science insights into practical applications for clinical care. Though large pharmaceutical companies are prominent in funding translational research, it may also occur at academic institutions and smaller start-up companies supported by venture capital. Drug product development research, which includes bioavailability studies and clinical trials to evaluate efficacy and safety, usually occurs in the private sector. According to the industry trade organization, spending by member companies exceeded \$70 billion in 2017;¹⁴ roughly one-fourth of domestic pharmaceutical sales were reinvested in domestic research and development.¹⁵ Clinical trials account for approximately two-thirds of industry research expenditures.¹⁶

One review found government resources have contributed, at least in part, to the discovery of over 150 marketed drugs and vaccines.¹⁷ The public sector's role in drug research is particularly notable with regard to the development of transformative drugs.¹⁸ In a study identifying the most transformative drugs approved in the United States over the past twenty-five years, we found that much of the discovery and translational work occurred at academic medical centers.¹⁹ In a cohort of 400 drugs approved between 1988 and 2005, about half had direct or indirect public-sector support.²⁰ That fraction was even higher—about two-thirds—for drugs that the FDA had given priority regulatory review because it considered them to be particularly

12. See Brian T. Bateman & Aaron S. Kesselheim, *Propofol as a Transformative Drug in Anesthesia: Insights from Key Early Investigators*, 20 *DRUG DISCOVERY TODAY* 1012, 1012 (2015); Evan S. Caplan & Aaron S. Kesselheim, *Anti-VEGF Therapy in Ophthalmology: a Qualitative Analysis of Transformative Drug Development*, 21 *DRUG DISCOVERY TODAY* 1019, 1019 (2016).

13. Iain M. Cockburn & Rebecca M. Henderson, *Publicly Funded Science and the Productivity of the Pharmaceutical Industry*, 1 *INNOVATION & POL'Y* 1, 18 (2000).

14. PHARM. RES. & MFRS. OF AM., 2018 PROFILE: BIOPHARMACEUTICAL RESEARCH INDUSTRY 4 (2018).

15. *Id.* at 5.

16. U.S. BUREAU OF LABOR STATISTICS., PRICE INDEXES FOR CLINICAL TRIAL RESEARCH: A FEASIBILITY STUDY (2014), <https://www.bls.gov/opub/mlr/2014/article/price-indexes-for-clinical-trial-research-a-feasibility-study.htm>.

17. Ashley J. Stevens, *The Role of Public-Sector Research in the Discovery of Drugs and Vaccines*, 364 *NEW ENG. J. MED.* 535, 538 (2011).

18. See Jonathan M. Spector et al., *Fundamental Science Behind Today's Important Medicines*, 10 *SCI. TRANSLATIONAL MED.* 1, 2 (2018) (noting that initial pharmaceutical research of a potential drug generally evolves after years of academic, often publicly funded, research).

19. Aaron S. Kesselheim & Jerry Avorn, *The Most Transformative Drugs of the Past 25 Years: A Survey of Physicians*, 12 *NATURE REV. DRUG DISCOVERY* 425, 425 (2013).

20. Bhaven N. Sampat & Frank R. Lichtenberg, *What Are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation?*, 30 *HEALTH AFF.* 332, 335 (2011).

important. Studies of drug-related patents and publications show even more expansive reliance on publicly funded research. One study found that, of new molecular entities approved from 2000 to 2009, about half had patents that cited to NIH-funded research conducted in academic medical centers, suggesting a strong link between private-sector drug patenting and NIH-funded biomedical innovation.²¹ Another study of publications related to drugs approved from 2010 to 2016 found that NIH funding could be linked through disclosures in those publications to every one of the new drugs approved by the FDA in this time period.²²

In light of these studies, Congress has a considerable impact on funding early innovation since it appropriates NIH budgets annually. In 2018, the NIH's budget was about \$37 billion, which is among the largest investments by any government in scientific research in the world. The 21st Century Cures Act promised to add \$4.8 billion to this total over ten years, but this funding depends on annual appropriation by Congress. This funding level grew substantially in the 1990s but has remained stagnant since then, when accounting for inflation; in fact, a 2018 study from the Congressional Research Service suggests that, after adjusting for inflation, estimated NIH funding for 2019 remains nearly 10% below 2003 funding levels.²³ Returning to annual increases and year-to-year certainty in the NIH budget will ensure continued opportunities for innovation in the pharmaceutical sector.

B. *Technology Transfer/Licensing*

When government-funded research in academic centers or government laboratories yields potentially valuable targets for therapy, those discoveries are often passed on to other institutions for further research, development, and commercialization.²⁴ Because patents are the primary means of assigning ownership and financial rewards related to drug products, this creates an important paradox: critical advances in basic and translational science, occurring in academic centers and government laboratories, may not be patentable.²⁵ In one case, academic patents on cell signaling pathway inhibition

21. Bhaven N. Sampat & Harold Alan Pincus, *Citations in Life Science Patents to Publicly Funded Research at Academic Medical Centers*, 8 CLINICAL & TRANSLATIONAL SCI. 759, 759 (2015).

22. Ekaterina Galkina Cleary et al., *Contribution of NIH Funding to New Drug Approvals 2010-2016*, 115 PROC. NAT'L ACAD. SCI. 2329, 2329 (2018).

23. JUDITH A. JOHNSON & KAVYA SEKAR, CONG. RES. SERV., NIH FUNDING FY1994-FY2019, at 4 (2018).

24. Bayh-Dole Act of 1980, Pub. L. No. 96-517, 94 Stat. 3015 [hereinafter Bayh-Dole Act].

25. See WENDY H. SCHACHT, CONG. RES. SERV., THE BAYH-DOLE ACT: SELECTED ISSUES IN PATENT POLICY AND THE COMMERCIALIZATION OF TECHNOLOGY 22 (2012) (noting significant backlash against institutions that seek patents early into the research process that led to increased regulation from the U.S. Patent and Trademark Office).

were ruled invalid.²⁶ In another case, the judge ruled a patent on a method of inhibiting the cyclooxygenase-2 enzyme invalid because the scientists had not isolated a product with this function, even though it later took a pharmaceutical manufacturer only six months to screen its compound library and identify such a product.²⁷

In 1980, Congress passed the Bayh-Dole Act (Bayh-Dole) to encourage further development and commercialization of federally-funded innovations.²⁸ Before that, patents obtained on federally-funded work as a default belonged to the federal government.²⁹ Some agencies worked out separate arrangements with individual academic institutions, but when the government did own the intellectual property, it was then tasked with licensing or transferring those discoveries for further development. Bayh-Dole allowed recipients of federal research funds, including universities, to obtain and exclusively license patents arising from federally funded research to small businesses and non-profit research organizations for further development³⁰ (a 1983 executive order expanded the reach of this technology transfer to include large corporations).³¹ By doing so, these institutions were encouraged to claim patent rights that could eventually result in commercialization of the inventions in the private sector. In the past three decades, there has been a significant expansion in academic patents obtained for drug products.³² However, trends towards increased academic patenting date back to before Bayh-Dole and there is also evidence that most technology transfer licenses include limited compensation for academic medical centers or the government,³³ with some notable exceptions (e.g., New York University and infliximab [Remicade],³⁴ the

26. *Ariad Pharm. v. Eli Lilly*, 598 F.3d 1336, 1355 (Fed. Cir. 2010).

27. *Univ. of Rochester v. GD Searle*, 358 F.3d 916, 920-21 (Fed. Cir. 2004).

28. Daniel J. Hemel & Lisa L. Ouellete, *Bayh-Dole Beyond Borders*, J. L. & BIOSCIENCES 282, 282-83 (2017).

29. Rebecca Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663, 1663 (1996).

30. Bayh-Dole Act.

31. Ronald Reagan, President's Memorandum to the Heads of the Executive Departments and Agencies, Government Patent Policy (Feb. 18, 1983).

32. Aaron S. Kesselheim, *An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences*, 89 MILBANK Q. 450, 454 (2011).

33. See Heidi Ledford, *Universities Struggle to Make Patents Pay*, 501 NATURE 471, 471 (2013); see also U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-03-829, TECHNOLOGY TRANSFER: NIH-PRIVATE SECTOR PARTNERSHIP IN THE DEVELOPMENT OF TAXOL 5, 9 (2003).

34. Maureen Farrell, *Universities That Turn Research into Revenue*, FORBES (Sep. 12, 2008), https://www.forbes.com/2008/09/12/google-general-electric-ent-tech-cx_mf_0912_universitypatent.html.

University of Minnesota and abacavir [Ziagen]),³⁵ few technology transfer licenses are extremely lucrative.

In recent decades, basic and translational science researchers and institutions have increasingly sought patents to protect their discoveries, such as research tools and biochemical targets such as genes or proteins. Such parties can then negotiate licensing contracts with downstream partners such as pharmaceutical companies, formalizing their intellectual contribution and in some cases receiving financial compensation. Conversely, patenting discoveries may hinder effective scientific collaborations, increase research costs, and promote secrecy.³⁶ It is far more lucrative for pharmaceutical companies to invest in products that provide clear intellectual property ownership without other restrictions on use.³⁷ In some cases, this may mean that intellectual property incentives do not always align with global disease burdens or unmet public health needs.³⁸

Licensing agreements for commercialization of government-funded research generally do not impose pricing restrictions on the marketed drug product, nor do they provide funding back to the NIH. For example, the licensing agreement between the University of Pennsylvania and Novartis over chimeric antigen receptor T-cell (CAR-T) therapy included upfront payments, payment for development milestones, and a new \$20 million on-campus facility,³⁹ but the University had no say over the initial price of \$475,000 for a single infusion of tisagenlecleucel [Kymriah].⁴⁰ Legislators, and even the director of the NIH, have suggested that the NIH could establish “payback” terms for drugs or technologies that were heavily developed with federally-funded patents.⁴¹ This happened in the case of the cancer drug paclitaxel (Taxol), as the NIH funded drug development, including five of six studies submitted for FDA approval. Bristol-Myers Squibb won the right to scale up

35. Greta Kaul, *Patently Lucrative: The Intellectual Property that Makes Big Money for the U*, MINNPOST (Feb. 4, 2018), <https://www.minnpost.com/education/2018/02/patently-lucrative-intellectual-property-makes-big-money-u>.

36. Michael Heller & Rebecca Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698 (1998).

37. See Shuai Xu & Aaron S. Kesselheim, *Medical Innovation Then and Now: Perspectives of Innovators Responsible for Transformative Drugs*, 42 J. L. MED. & ETHICS 564, 569 (2014) (remarking on “the not-invented-here syndrome.”).

38. *See id.*

39. Wendy Diller, *In New Industry-Academic Model, Big Pharma Partners with University Researchers*, IN VIVO (Dec. 10, 2012), <https://www.elsevier.com/connect/penn-and-novartis-collaborate-on-new-cancer-drug>.

40. Ed Silverman, *At \$475,000, New Cancer Drug Raises Thorny Questions About Drug Pricing and Value*, STAT NEWS (Sept. 4, 2017), <https://www.statnews.com/2017/09/04/cancer-drug-pricing-novartis>.

41. Carolyn L. Treasure et al., *Do March-In Rights Ensure Access to Medical Products Arising from Federally Funded Research? A Qualitative Study*, 93 MILBANK Q. 761, 782 (2015).

production and, by contract, was to pay 0.5% of worldwide revenues to the NIH.⁴² The agency received a total of \$35.3 million in royalties, in exchange for government commitments of \$80 million for research and development and Medicare payments of nearly \$700 million for paclitaxel from 1994-1999 alone.⁴³ Given the essential early investor role played by public funds, there ought to be greater reinvestment in the NIH and other federal agencies from the pharmaceutical industry when innovations derived from federal funding result in extremely lucrative final products.

C. Tax Breaks for Research Funding

To incentivize great research and development by pharmaceutical companies, the government indirectly subsidizes such activities, in the form of lost tax revenue, via several tax incentives that often significantly reduce the tax burden of those companies. According to the U.S. Treasury, the chemical and pharmaceutical industries had average effective tax rates of 22% from 2007-11 (most industries ranged from 15-27%).⁴⁴ Tax credits that benefit the drug industry include the research and experimentation tax credit,⁴⁵ the Orphan Drug Act tax credit (which until 2018 covered 50% and now covers 25% of research and development costs),⁴⁶ in addition to grants and waived FDA fees. Finally, pharmaceutical companies benefit from deferred taxation of foreign revenues until those revenues are repatriated into the United States.⁴⁷ The research and experimentation tax credit was introduced in 1981,⁴⁸ offering a credit of 20% for all “qualified research expenses” that exceed the Alternative Simplified Credit base amount of 14%.⁴⁹ The research and experimentation tax credit was recently made permanent,⁵⁰ and some in Congress have sought to increase the Alternative Simplified Credit to 20%.⁵¹

To maximize their foreign tax credits, many drug companies have undergone corporate inversion, a process in which they merge and reincorporate in countries with lower (or no) tax burden.⁵² Ireland, which has a

42. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 33, at 1, 4.

43. *Id.* at 15, 17.

44. U.S. DEP'T OF THE TREASURY, AVERAGE EFFECTIVE FEDERAL CORPORATE TAX RATES 1-2 (2016).

45. 26 U.S.C. § 41 (2017).

46. Tax Cuts and Jobs Act of 2017, Pub. L. No. 115-97, 131 Stat. 2054.

47. CONG. BUDGET OFFICE, AN ANALYSIS OF CORPORATE INVERSIONS 4 (2017).

48. Economic Recovery Tax Act, 95 Stat. 172 (1981).

49. Credit for Increasing Research Activities, 26 U.S.C. § 41 (2018).

50. Protecting Americans from Tax Hikes (PATH) Act, Pub. L. No. 114-113, 129 Stat. 2242 (2015).

51. Research and Experimentation Advances Competitiveness at Home (REACH) Act, H.R. 5187, 114th Cong. (2016).

52. CONG. BUDGET OFFICE, *supra* note 47, at 9.

12.5% corporate tax rate, is now the leading exporter of pharmaceuticals to the United States. The government has been opposed to such arrangements, as they deprive the treasury of significant tax revenue; a blocked 2016 Pfizer-Allergan merger was reportedly valued at \$160 billion.⁵³ In addition, many drug companies hold revenues overseas; at the end of 2014, the top eight pharmaceutical companies based in the United States held close to \$500 billion in revenues overseas (Pfizer had the most, estimated at \$193.6 billion).⁵⁴ The Tax Cuts and Jobs Act of 2018 (TCJA) lowered the baseline corporate tax rate to 21% while significantly discounting repatriation tax rates, in hopes of curbing inversion and returning revenues to the United States for domestic investment.⁵⁵ Early evidence suggests that the TCJA has provided outsized returns to pharmaceutical corporations and investors, in the form of stock buybacks and dividends among other methods.⁵⁶

D. *Costs/Risks of Drug Discovery*

A challenge in determining whether, and to what extent, the federal government ought to assist pharmaceutical companies in research and development relates to disputes as to the actual cost of new drug development. A frequently-cited study, from the industry-funded Tufts Center for the Study of Drug Development, estimated a cost of \$2.6 billion for a pharmaceutical manufacturer to develop a new drug, in addition to \$312 million for post-approval research.⁵⁷ However, this projection was based on an undisclosed, highly-selected group of drugs and represented a significant increase from the Center's previous estimated cost of \$802 million in 2003.⁵⁸ Re-analyses of the 2003 figure suggest that the true cost of new drug development was actually

53. Caroline Humer & Ransdell Pierson, *Obama's Inversion Curbs Kill Pfizer's \$160 Billion Allergan Deal*, REUTERS (April 6, 2016), <http://www.reuters.com/article/us-allergan-m-a-pfizer-idUSKCN0X21NV>.

54. CITIZENS FOR TAX JUSTICE, FORTUNE 500 COMPANIES HOLD A RECORD \$2.4 TRILLION OFFSHORE (2016), <http://ctj.org/pdf/pre0316.pdf>.

55. See Michael S. Sinha & Aaron S. Kesselheim, *The Tax Cut and Jobs Act of 2017 and the Pharmaceutical Industry*, 46 J. L. MED. & ETHICS 806, 806 (2018).

56. *Id.* at 806-08; see AMERICANS FOR TAX FAIRNESS, BAD MEDICINE: HOW GOP TAX CUTS ARE ENRICHING DRUG COMPANIES, LEAVING WORKERS & PATIENTS BEHIND 1 (2018), <https://americansfortaxfairness.org/wp-content/uploads/Pharma-Tax-Cut-Report-4.26.18-FINAL-.pdf>.

57. TUFTS CTR. FOR THE STUDY OF DRUG DEV., COST TO DEVELOP AND WIN MARKETING APPROVAL FOR A NEW DRUG IS \$2.6 BILLION 1-2 (2014); Jerry Avorn, *The \$2.6 Billion Pill – Methodologic and Policy Considerations*, 372 NEW ENG. J. MED. 1877, 1877-79, (2015).

58. TUFTS CTR. FOR THE STUDY OF DRUG DEV., *supra* note 57, at 1-2; Avorn, *supra* note 57, at 1877.

between \$115 to \$240 million;⁵⁹ if a non-highly-selected group of compounds was used, the number was \$161 million.⁶⁰ In addition, approximately half of the \$2.6 billion estimate was obtained by compounding the cost of capital at 10.6% annually.⁶¹ The substantial differences in these estimates affect the way we perceive a governmental obligation to continue lucrative arrangements with the pharmaceutical industry while continuing a practice of noninterference in drug pricing, despite the government being a central payor for high-priced drugs.

It is well-known that the process of drug development is inherently risky, with hundreds of compounds screened and taken through pre-clinical development before a much smaller subset enters clinical trials. About 85% of drug research projects fail before they are tested in human clinical trials.⁶² By industry analysis, for every 5000 compounds screened, 5 make it to clinical trials and 1 becomes an approved drug.⁶³ The term “valley of death” (the time between the development of a key scientific insight and the availability of a resulting drug product)⁶⁴ was coined to indicate that there is less government and venture capital funding for this phase of development due to increasing costs and risks. However, follow-on drug development takes advantage of the transformative scientific developments that established lucrative targets and mechanisms of action. Developing a drug with a non-novel mechanism of action substantially narrows the initial compound library, lowering research costs while increasing the likelihood of success as compared to the development of drugs with novel mechanisms of action.⁶⁵ This common phenomenon has been seen for antibiotics, statin cholesterol drugs, and proton-pump inhibitors for gastrointestinal reflux, among others.

In 2012, the NIH created a unit to facilitate the development of new drugs, called the National Center for Advancing Translational Sciences.⁶⁶ It was specifically designed to allow NIH to absorb more of the costly, risky

59. WORLD HEALTH ORG., PUBLIC HEALTH, INNOVATION AND INTELLECTUAL PROPERTY RIGHTS 76 (2006), <http://www.who.int/intellectualproperty/documents/theroport/ENPublicHealthReport.pdf>.

60. PUBLIC CITIZEN, RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R&D “SCARE CARD” 19 (2001), <https://www.citizen.org/sites/default/files/rdmyths.pdf>.

61. Avorn, *supra* note 57, at 1878.

62. Isabella Mak et al., *Lost in Translation: Animal Models and Clinical Trials in Cancer Treatment*, 6 AM. J. TRANSLATIONAL RES. 114, 114-18 (2014).

63. FDA, THE BEGINNINGS: LABORATORY AND ANIMAL STUDIES (2015), <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143475.htm>.

64. Declan Butler, *Translational Research: Crossing the Valley of Death*, 453 NATURE 840, 840-42 (2008).

65. Joseph DiMasi & Cherie Paquette, *The Economics of Follow-On Drug Research and Development: Trends in Entry Rates and the Timing of Development*, 22 PHARMACOECONOMICS 1, 1-14 (2004).

66. NAT'L INST. OF HEALTH, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIENCES, <http://www.ncats.nih.gov> (last visited Mar. 30, 2019).

translational work of drug development, enabling products likely to be effective in humans to be handed off to the pharmaceutical industry for final pre-clinical testing, clinical trials, and commercialization.⁶⁷ Critics argued that this amounted to “socializing the risk” and privatization of profit.”⁶⁸ Given the significant public sector contributions to drug development described herein, the presidential administration’s initial FY2018 budget proposed cuts to the NIH and other federal scientific research agencies that threatened to drastically limit the continued development of transformative lifesaving medications (though they were ultimately not enacted).⁶⁹

II. EVALUATION AND FDA REVIEW OF NEW DRUG APPLICATIONS

A. *Preclinical Testing*

The first step of the pathway to an FDA-approved drug is preclinical testing, which includes synthesis, purification, target identification, screening, confirmation of potential for safety and effectiveness, chemical analysis and manufacturing controls, and laboratory (*in vitro*) and animal (*in vivo*) toxicity testing. Preclinical testing, in other words, reflects the entire process of evaluating a compound prior to exposing it to human subjects, and is a time period with a high failure rate. There is ongoing controversy over reproducibility and reliability of preclinical data, with some suggesting it is a reason why so many drugs fail during clinical trials.⁷⁰ The FDA’s Animal Handling Procedures outline some principles for preclinical research testing practices,⁷¹ and the Animal Welfare Act of 1966 established guidelines and principles for the use of animal models in research experimentation.⁷²

An Investigational New Drug (IND) application to the FDA is a prerequisite to initiating human clinical testing; the IND automatically takes

67. NAT’L CENTER FOR ADVANCING TRANSLATIONAL SCIENCES, “APRIL 24, 2012: ACTING DIRECTOR’S MESSAGE” (last visited May 11, 2019), <https://ncats.nih.gov/director/april-2012> (last visited April 28, 2019).

68. Jonathan Kahn, *Privatizing Biomedical Citizenship: Risk, Duty, and Potential in the Circle of Pharmaceutical Life*, 15 MINN. J. L. SCI. & TECH. 791, 793 (2014).

69. See DEP’T OF HEALTH AND HUM. SERV., PUTTING AMERICA’S HEALTH FIRST; FY 2018 PRESIDENT’S BUDGET FOR HHS 2 (2017), https://www.hhs.gov/sites/default/files/Consolidated%20BIB_ONLINE_remediated.pdf.

70. Thomas Steckler T, *Preclinical Data Reproducibility for R&D: The Challenge for Neuroscience*, 4 SPRINGERPLUS 1, 1-4 (2015).

71. Transportation, Sale, and Handling of Certain Animals: Congressional Statement of Policy, 7 U.S.C. § 2131 (2011).

72. Animal Welfare Act, Pub. L. No. 89-544, 80 Stat. 350-52 (codified as amended in 7 U.S.C. § 2131-2156).

effect 30 days after submission unless the FDA imposes a “clinical hold.”⁷³ A clinical hold is issued when risks are unreasonable and if there seems to be significant risk of illness or injury, if investigators are not qualified, or if the submitted protocols are deficient in design to meet objectives.⁷⁴ Though a clinical hold may temporarily stop studies on a compound, research will resume after satisfactorily addressing the FDA’s concerns. Among INDs submitted between October 2012 and September 2013, 9% of IND applications were placed on clinical holds (125/1410), and of those, more than half came off clinical hold within one year.⁷⁵ Once the IND goes into effect, safety reporting regulations require investigators to gather and report significant adverse events that occur during human clinical trials, with reporting of significant unexpected adverse events within fifteen days.⁷⁶

B. *Clinical Trials*

Upon identifying a promising compound has been identified, the process of testing begins, culminating in the submission of a new drug application (NDA) to the FDA.⁷⁷ Pharmaceutical companies traditionally conduct these studies, though the extent of evidence required to demonstrate safety and efficacy often varies considerably depending on the type of drug and its intended indications.

Drugs are usually tested in up to three phases of clinical trials prior to regulatory approval: Phase I, which provides a first screen for toxicity (usually in healthy volunteers);⁷⁸ Phase II, used for dose-ranging safety studies and initial proof of concept in the patients intended to be treated;⁷⁹ and Phase III, which usually involves large, randomized, controlled clinical trials intended to establish drug efficacy.⁸⁰ The key trials providing the basis for the FDA’s affirmation of efficacy are called the “pivotal trials.”

Data on the clinical trial process suggest that it takes about six to nine years on average from IND submission to FDA approval; Phase I averages 21.6

73. FDA, INDIVIDUAL PATIENT EXPANDED ACCESS APPLICATIONS: FORM FDA 3926: GUIDANCE FOR INDUSTRY 6 (2017), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm432717.pdf>.

74. U.S. DEP’T OF HEALTH & HUM. SERVS., IND APPLICATION PROCEDURES: CLINICAL HOLD (2015), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362971.htm>.

75. U.S. DEP’T OF HEALTH & HUM. SERVS., HOW DO CLINICAL HOLDS IMPACT DRUG DEVELOPMENT PROGRAMS? (2016), <https://www.fda.gov/Drugs/NewsEvents/ucm514825.htm>.

76. 21 C.F.R. § 312.64(b) (2016).

77. Applications for FDA Approval to Market a New Drug or an Antibiotic Drug, 21 C.F.R. § 314 (2018).

78. 21 C.F.R. § 312.21(a) (2015).

79. *Id.* § 312.21(b).

80. *Id.* § 312.21(c).

months, Phase II averages 25.7 months, and Phase III averages 30.5 months.⁸¹ In a sample of pivotal trials of new drugs approved in a recent eight-year period, only one-third of pivotal trials last longer than six months, even when testing drugs intended for chronic use.⁸² Over half of all pivotal trials test a new drug against placebo rather than an active comparator. In addition, nearly half of all pivotal trials rely upon surrogate measures or biomarkers (markers of disease such as changes in laboratory tests or radiology reports) as endpoints, as opposed to clinical outcomes (such as end-organ damage, mortality, or changes in symptoms).⁸³

The cost of clinical trials has been increasing, requiring greater investment per new drug approved.⁸⁴ Most funding for clinical trials comes from pharmaceutical manufacturers, with Phase III trials being most expensive. A 2015 industry report puts average Phase III per-patient costs at \$42,000.⁸⁵ In that review, oncology trials were the most expensive, estimated to cost \$69,000 per Phase III trial participant. When accounting for the number of enrollees in pivotal trials, data emerging from FDA-approved drugs in 2015-2016 showed that the median total trial cost was \$19 million.⁸⁶

In recent years, many drug companies have outsourced their clinical trials to other countries. In one cancer trial, costs were \$100,000 per patient in the US, but \$10,000 per patient in China.⁸⁷ There is debate as to whether rising clinical trial costs are related to inefficiencies in the process of conducting what are often multicenter trials (e.g. the need for multiple institutional review board approvals) versus the increasing complexity and cost of drug discovery. In the 1997 FDA Modernization Act,⁸⁸ the FDA was directed to consult with sponsors to negotiate terms of clinical trial design and enrollment size sufficient to support an NDA. The terms of such industry consultations are

81. See Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 165 (2003).

82. Nicholas Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents*, 311 J. AM. MED. ASS'N 368, 368-77 (2014).

83. *Id.*

84. Ernst R. Berndt & Iain M. Cockburn, *Price Indexes for Clinical Trials Research: a Feasibility Study* 4-5 (Nat'l Bur. Lab. & Econ., Working Paper No. 18918, 2014).

85. PHARM. RES. & MFRS. OF AM., BATTELLE TECHNOLOGY PARTNERSHIP PRACTICE, BIOPHARMACEUTICAL INDUSTRY-SPONSORED CLINICAL TRIALS: IMPACT ON STATE ECONOMIES 6 (2015), <http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>.

86. Thomas J. Moore et al., *Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016*, 178 J. AM. MED. ASS'N INTERNAL MED. 1451, 1451-57 (2018).

87. Joanne Nicholas, *Outsourcing Clinical Trials*, 104 J. NAT'L CANCER INST. 1043, 1043-45 (2012).

88. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

documented as part of a “special protocol assessment,”⁸⁹ a written agreement on the type and outcome of studies that would lead to approval unless a “substantial scientific issue” arises.⁹⁰ There has been controversy about the extent to which cost considerations contribute to bias in study design and interpretation of results, with industry funders preferring comparators or other aspects of trial design that allow the trial to be conducted at a lower cost with greater odds of a favorable outcome. Adaptive trial designs, which will be discussed later, could allow greater flexibility and efficiency, cutting cost and duration of clinical trials, although such trial designs if not implemented carefully also risk impeding collection of robust data while biasing study findings.⁹¹

Data collected about a drug in preclinical studies and clinical trials ultimately comprise the basis of an NDA submission to the FDA. Approval is granted if, based on the observation of “substantial evidence” arising from “adequate and well-controlled clinical investigations” and adequate tests by all methods “reasonably applicable” show that the drug is safe for use.⁹² The FDA traditionally preferred two Phase III trials for approval, the rationale being that the results of a single trial “may be subject to unanticipated, undetected systematic biases” or occur by chance alone.⁹³ But in 1997, FDAMA included language that explicitly allowed demonstration of efficacy by “one adequate and well-controlled clinical investigation,” along with confirmatory evidence.⁹⁴ Now, a single pivotal trial forms the basis of approval for between one-third and one-half of all new drugs, particularly cancer drugs, biologics, and drugs for rare diseases.⁹⁵ Pivotal trials do not need to show results that are statistically significant (since drugs can be approved based on single-arm studies) or clinically significant (since drugs can be tested against placebos). The FDA Animal Rule exists to allow studies in animals to form the basis of

89. FDA, SPECIAL PROTOCOL ASSESSMENT: GUIDANCE FOR INDUSTRY 1 (2016), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM498793.pdf>.

90. 21 U.S.C. § 355(b) (2016).

91. Laura Bothwell & Aaron Kesselheim, *The Real-World Ethics of Adaptive-Design Clinical Trials*, 47 HASTINGS CTR. REP. 27, 27-37 (2017); John Kairalla, *Adaptive Trial Designs: A Review of Barriers and Opportunities*, 13 TRIALS 1, 1-9 (2012).

92. 21 U.S.C. § 355(d) (2016).

93. FDA, PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 4 (1998), <http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf>.

94. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

95. Nicholas Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents*, 311 J. AM. MED. ASS'N 368, 368-77 (2014); Zachary Brennan, *Almost Half of All New Drug Approvals in 2018 Relied on One Clinical Trial*, REGULATORY FOCUS (May 14, 2019), <https://www.raps.org/news-and-articles/news-articles/2019/5/almost-half-of-all-new-drug-approvals-in-2018-reli>.

approval in rare situations in which conducting human efficacy studies would be unethical, such as for bioterrorism countermeasures.⁹⁶

Clinical trial data submitted to the as part of an NDA is considered to be a trade secret and therefore not publicly available, even after the drug is approved.⁹⁷ But in the past, manufacturers selectively published only positive trials from those submitted to FDA while suppressing negative trials.⁹⁸ In 2007, FDAAA required that all clinical trial protocols and results be posted publicly on a federally-maintained and publicly available website, ClinicalTrials.gov. Results reporting has been inconsistent,⁹⁹ but a recent study of clinical trials supporting approval for drugs to treat diabetes and cardiovascular disease found an association between mandated trial reporting and increased trial registration, publication of results, and outcome reporting in ClinicalTrials.gov.¹⁰⁰ Evidence suggests that the process is improving over time; a separate study found good concordance between information found on ClinicalTrials.gov and Drugs@FDA.¹⁰¹ Some manufacturers have experimented with systems for promoting clinical trial data transparency, as have some medical journals by enacting data transparency rules for trials that they publish.¹⁰²

Use of surrogate measures as endpoints for pivotal clinical trials has become prevalent, although it is a controversial practice. Surrogate measures can allow investigators to observe outcomes in diseases for which actual clinical outcomes may be observed only after many years, as with Alzheimer's disease. But numerous drugs approved or used widely by physicians based on evidence from surrogate measures have later been proven to be unsafe or not to translate to improved clinical outcomes.¹⁰³ In advanced breast cancer, bevacizumab (Avastin) delayed tumor progression but did not prolong overall

96. FDA, PRODUCT DEVELOPMENT UNDER THE ANIMAL RULE: GUIDANCE FOR INDUSTRY I (2015).

97. Aaron Kesselheim & Michelle Mello, *Confidentiality Laws and Secrecy in Medical Research: Improving Public Access to Data on Drug Safety*, 26 HEALTH AFF. 483, 483-91 (2007).

98. Arthur Feldman et al., *Publishing "Invisible" and "Abandoned" Clinical Trials: A Commitment for CTS*, 6 CLINICAL TRANSLATIONAL SCI. 251, 251 (2013).

99. See *id.* at 251-53.

100. Adam Phillips et al., *Association of the FDA Amendment Act with Trial Registration, Publication, and Outcome Reporting*, 18 TRIALS 1, 1-10. (2017).

101. Lisa Schwartz et al., *ClinicalTrials.gov and Drugs@FDA: A Comparison of Results Reporting for New Drug Approval Trials*, 165 ANNALS INTERNAL MED. 421, 421-30 (2016).

102. Michelle Mello et al., *Preparing for Responsible Sharing of Clinical Trial Data*, 369 NEW ENG. J. MED. 1651, 1651-58 (2013); Darren Taichman et al., *Sharing Clinical Trial Data: A Proposal from the International Committee of Medical Journal Editors*, 374 NEW ENG. J. MED. 384, 384-86 (2016).

103. Staffan Svensson et al., *Surrogate Outcomes in Clinical Trials: A Cautionary Tale*, 173 J. AM. MED. ASS'N INTERNAL MED. 611, 611-12 (2013).

survival and was associated with important adverse effects.¹⁰⁴ In spite of robust lowering of hemoglobin A1c levels in diabetic patients taking rosiglitazone (Avandia), the drug was found to increase their risk of myocardial infarction.¹⁰⁵ Finally, bedaquiline (Sirturo) was approved in 2012 for multi-drug resistant tuberculosis; the drug was approved on the basis of a surrogate endpoint, even though patients randomized to receive the drug had a three-fold higher rate of death, mostly from tuberculosis.¹⁰⁶ While testing a drug's effect on a surrogate measure—such as the biomarker of A1c or sputum conversion—can make drug testing more efficient and less expensive to the manufacturer, it may not always result in improved patient outcomes.

C. Regulatory Process

Once the data are aggregated and a manufacturer believes it has adequate evidence to demonstrate safety and efficacy in treating a particular condition, it submits an NDA to the FDA for consideration. The process for evaluating an NDA can involve dozens of FDA scientists from toxicological, statistical, medical, and other specialties reviewing the studies in animals, preclinical results, and clinical trials. The FDA may also convene a group of outside experts, or an “advisory committee,” to provide guidance on approval decisions.¹⁰⁷ The advisory committee deliberates and makes numerous recommendations, often including whether the NDA should be approved; the FDA follows the advisory committee's recommendations in about three-quarters of cases.¹⁰⁸ Complex conflict-of-interest rules apply to advisory committee members necessitating full disclosure and sometimes excluding members from serving, although waivers can be obtained.¹⁰⁹ There is some evidence to suggest that advisory committee members' votes may be impacted by their financial relationships, but this remains controversial.¹¹⁰

104. Susan Pories et al., *Evidence for the Role of Bevacizumab in the Treatment of Advanced Metastatic Breast Cancer: A Review*, 2 *BREAST CANCER* 37, 37-44 (2010).

105. Gardiner Harris, *Report Backs Up Warnings About Drug Avandia*, N.Y. TIMES, July 27, 2007, at A19.

106. Gregory Fox & Dick Menzies, *A Review of the Evidence for Using Bedaquiline (TMC207) to Treat Multi-Drug Resistant Tuberculosis*, 2 *INFECTIOUS DISEASES & THERAPY* 123, 123-44 (2013).

107. FDA., *ADVISORY COMMITTEES* (2016), <http://www.fda.gov/AdvisoryCommittees/default.htm>.

108. Matthew Herper, *The FDA Ignores Its Advisors a Quarter of the Time*, FORBES (Oct. 12, 2010), <https://www.forbes.com/sites/matthewherper/2010/10/12/the-fda-ignores-its-advisors-a-quarter-of-the-time>.

109. FDA, *supra* note 107.

110. Genevieve Pham-Kanter, *Revisiting Financial Conflicts of Interest in FDA Advisory Committees*, 92 *MILBANK Q.* 446, 446-70 (2014); Jing Xu et al., *Association of Appearance of Conflicts of Interest With Voting Behavior at FDA Advisory Committee Meetings: A Cross-Sectional Study*, 177 *J. AM. MED. ASS'N INTERNAL MED.* 1038, 1038-40 (2017).

In the 1980s, the drug review process was slow, in large part due to limited FDA funding leading to a lack of sufficient human resources.¹¹¹ In response, the pharmaceutical industry and Congress developed a new approach for funding the agency, by which user fees would accompany submission of an NDA. The first Prescription Drug User Fee Act (PDUFA) was enacted in 1992,¹¹² and the resulting increase in FDA's personnel budget made it possible to evaluate drugs more quickly; review times fell from the pre-PDUFA average of thirty-one months, and a spike in new drug approvals after 1992 resulted from clearing the pre-PDUFA backlog.¹¹³ Annual drug approvals subsequently returned to their historic mean, although there has been an uptick in approvals in the past several years.¹¹⁴ As part of the user fee arrangement, the FDA is held to review deadlines for approving or rejecting new drug applications—twelve months (later shortened to ten) for typical applications and six months for “priority review” applications, which the FDA attaches to drugs that represent an therapeutic advance over existing therapy.¹¹⁵

As a result of these deadlines—which the FDA met for all fifty-nine of its 2018 NDA approvals—the FDA is now one of the fastest drug regulatory agencies in the world and routinely approves new drugs sooner than Canada or Europe, with annual review times of about eight to ten months on average across all new drugs.¹¹⁶ However, some data suggest that faster approvals may have increased the rate of post-approval safety events, including one study that showed that approval decisions made closer to the arbitrarily-imposed regulatory review deadlines were associated with subsequent safety-related labeling changes or withdrawals of the drug from the market.¹¹⁷ Some studies

111. JANET WOODCOCK & SUZANNE JUNOD, FDA, PDUFA LAYS THE FOUNDATION: LAUNCHING INTO THE ERA OF USER FEE ACTS 9 (2011), <https://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/FOrgsHistory/EvolvingPowers/UCM593453.pdf>.

112. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified at 21 U.S.C. § 379).

113. Kenneth I. Kaitin, *The Prescription Drug User Fee Act of 1992 and the New Drug Development Process*, 4 AM. J. THERAPEUTICS 167, 169-70 (1997).

114. Jonathan J. Darrow & Aaron S. Kesselheim, *Drug Development and FDA Approval, 1938-2013*, 370 NEW ENG. J. MED. (2014), <https://www.nejm.org/doi/full/10.1056/NEJMp1402114>.

115. Joseph S. Ross & Aaron S. Kesselheim, *FDA Policy and Cardiovascular Medicine*, 132 CIRCULATION 1136, 1137-38 (2015).

116. FDA, FDA AND ACCELERATING THE DEVELOPMENT OF NEW PHARMACEUTICAL THERAPIES 2 (2015), <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM439183.pdf>; Nicholas S. Downing et al., *Regulatory Review of Novel Therapeutics—Comparison of Three Regulatory Agencies*, 366 NEW ENG. J. MED. 2284, 2288-91 (2012).

117. Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 J. AM. MED. ASS'N, 1854, 1862 (2017).

have found associations with reports of serious safety events,¹¹⁸ although other reviews have found no such association.¹¹⁹

The FDA may now take up to two months before a review starts to ensure that the drug application is in order. Non-approvals can sometimes occur due to insufficient data or concerns about the NDA; in some cases, these issues are then fixed and the drug is approved on a second cycle of review. The FDA approved 95% of 2018 NDAs on the first cycle, representing a sharp increase from 2010, when first action approvals were at 56%.¹²⁰

The current NDA user fee is around \$2.6 million per drug.¹²¹ User fees were initially limited to funding the FDA's NDA review apparatus. Starting in 2007, the law allowed FDA to apply user fees to drug safety analyses, but the vast majority still goes to support drug review activities.¹²² User fees overall account for over \$2 billion annually, about 40% of the FDA's budget.¹²³ PDUFA must be renewed every five years, which provides an occasion for other FDA policymaking, as legislators now consider it a must-pass piece of legislation. Discussions about the content of the PDUFA renewal tends to occur anywhere from two to three years prior to the renewal deadline and the framework of the draft legislation is often presented to Congress as a negotiated agreement between FDA and industry. The sixth and most recent iteration of the law is the FDA Reauthorization Act of 2017.¹²⁴

D. Expedited Development and Review

Apart from the priority review designation, which speeds FDA review times for certain drugs that represent therapeutic advances over currently available treatments, four other pathways have been created to hasten the drug development process: (1) the Orphan Drug Act (1983) provides a special designation for drugs for rare diseases, and the FDA has traditionally applied maximal flexibility to pivotal trial design for these drugs, with many now approved on the basis of single-arm studies and surrogate measures; (2) the

118. Daniel Carpenter et al., *Drug-Review Deadlines and Safety Problems*, 358 *NEW ENG. J. MED.*, 1354, 1360 (2008); Downing, *supra* note 117, at 1862.

119. Henry Graboswk & Y. Richard Wang, *Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patient Safety? An Analysis of the 1992 Prescription Drug User Fee Act*, 51 *J. L. & ECON.*, 377, 401 (2008).

120. Janet Woodcock, *2018: A Year of Innovation, Efficiency, and New Advances in Drug Therapy for the American Public*, FDA: FDA VOICES (Jan. 7, 2019), <https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm629275.htm>.

121. Prescription Drug User Fee Rates for Fiscal Year 2019, 83 *Fed. Reg.* 37504, 37507 (Aug. 1, 2018).

122. Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, § 101, 121 *Stat.* 823.

123. FDA, *FDA AT A GLANCE 1-2* (2017), <https://www.fda.gov/media/104402/download>.

124. FDA Reauthorization Act, Pub. L. No. 115-52, 131 *Stat.* 1005 (2017).

Fast Track pathway (1988) allows approval based on one Phase II trial that produces sufficient safety and efficacy data; (3) the Accelerated Approval pathway (1992) allows approval based on surrogate measures that are only “reasonably likely” to predict patient benefit; and (4) the Breakthrough Therapy pathway (2012) allows practices “intended to expedite development and review,” including early meetings to clarify requirements, involvement of senior officials in the review process, assignment of a cross-disciplinary project lead, and collaboration to ensure that clinical trials are designed as efficiently as practicable.¹²⁵

In one review of drugs approved between 1987 and 2014, there was a substantial increase in the number of expedited development and review programs associated with each newly approved agent, including a greater proportion of approved drugs that made use of at least one such program.¹²⁶ Driving this trend is an increasing proportion of non-first-in-class drugs (drugs with non-novel mechanisms of action) using at least one such program. Some evidence suggests that less robust clinical trial requirements for these expedited development pathways can be problematic. For example, a recent FDA report highlighted twenty-two cases in which Phase II and Phase III results diverged, suggesting that many drugs approved based on Phase II pivotal trials may later be determined to be unsafe or ineffective, making approval on the basis of a single Phase II trial alone concerning.¹²⁷ Patterns of irreproducibility of clinical trial findings across the research portfolio of a single drug affirm the value of the FDA’s traditional preference for manufacturers to conduct more than one pivotal trial.¹²⁸

E. *Further Innovations in the Development and Approval Process*

Recent policymaking has targeted changes to the processes and standards for FDA evaluation based on the presumption that such changes are necessary to accelerate innovation and improve patient access.¹²⁹ However, limiting the FDA’s ability to carefully review NDAs could also reduce the quality and

125. FDA, GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS (2014).

126. Aaron S. Kesselheim et al., *Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987–2014: Cohort Study*, BRIT. MED. J. 1, 1 (2015).

127. FDA, 22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS 2 (2017), <https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm535780.pdf>.

128. See e.g., Spencer Phillips Hey et al., *Success, Failure, and Transparency in Biomarker-Based Drug Development: A Case Study of Cholesteryl Ester Transfer Protein Inhibitors*, 10 CIRCULATION CARDIOVASCULAR QUALITY & OUTCOMES 1, 1 (2017).

129. James T. O’Reilly, *Losing Deference in the FDA’s Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939, 957–58 (2008).

safety of approved products, denigrating the value of FDA approval.¹³⁰ Drugs approved via expedited programs could result in post-approval safety events, leading to FDA drug safety communications and labeling updates, new boxed warnings about critical safety signals, or even market withdrawals of unsafe or ineffective drugs.¹³¹

Efficient new approaches to conducting randomized clinical trials are being proposed and put into practice. “Adaptive design trials” allow preliminary results to be assessed at pre-set interim points; study design can then be modified based on emerging early findings, with the intention of increasing trial efficiency and reducing patient allocation into seemingly less favorable treatment arms.¹³² Ethical and economic considerations compel limiting clinical trial enrollment to as few patients as is necessary to ascertain which treatment is preferable, but adaptive designs are controversial because their conclusions may be less valid or more subject to manipulation.¹³³ As mandated by the 21st Century Cures Act, the FDA updated its guidance for industry on adaptive design trials in September 2018.¹³⁴

Advances in biochemistry and genetics have also opened up the potential for new surrogate measures. Precision medicine aims to leverage insights from basic biology and genetics to identify predictive biomarkers and diagnostic tests that can improve the efficiency of therapeutic development and tailor treatments to individual patients.¹³⁵ The Precision Medicine Initiative was created as part of the 21st Century Cures Act and encourages the FDA to increase reliance on biomarkers and surrogate measures, as opposed to clinical endpoints, when assessing efficacy for drugs and devices.¹³⁶

“Adaptive licensing” has been advocated as a prospectively planned, flexible approach to approval, a compromise between expeditious drug approval and the time-consuming process of obtaining high quality data about the drug’s safety and efficacy. Through iterative phases of evidence-gathering, adaptive licensing allows for earlier but restricted access to medications for a limited group of patients in whom more efficacy and safety data can be

130. Aaron S. Kesselheim & Jerry Avorn, *New “21st Century Cures” Legislation: Speed and Ease vs Science*, 317 J. AM. MED. ASS’N. 581, 582 (2017).

131. Nicholas S. Downing, et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 J. AM. MED. ASS’N. 1854, 1861-62 (2017).

132. Laura E. Bothwell, et al., *Adaptive Design Clinical Trials: A Review of the Literature and ClinicalTrials.gov.*, BRIT. MED. J. OPEN. 1, 1 (2018).

133. See Laura E. Bothwell & Aaron S. Kesselheim, *The Real-World Ethics of Adaptive-Design Clinical Trials*, 47 HASTINGS CTR. REP. 27, 33-34 (2017).

134. See generally FDA, ADAPTIVE DESIGNS FOR CLINICAL TRIALS OF DRUGS AND BIOLOGICS: GUIDANCE FOR INDUSTRY (2018).

135. Spencer P. Hey & Aaron S. Kesselheim, *Countering Imprecision in Precision Medicine*, SCI. 448, 448-49 (2016).

136. THE WHITE HOUSE, PRECISION MEDICINE INITIATIVE, <https://obamawhitehouse.archives.gov/precision-medicine>.

gathered.¹³⁷ It thus seeks to balance timely access for patients with the need to assess and provide evolving information on benefits and harms. In this way, adaptive licensing aims to help health care providers arrive at better-informed decisions relating to patient care. It has been proposed as a response to the binary “go/no-go” regulatory approval decision in which, in its most extreme form, a drug is either available to everyone or no one. It was recently tested in limited situations in Europe.¹³⁸

A somewhat different approach to loosening approval standards is featured in the 21st Century Cures Act’s Limited Population Pathway. A provision of the law known as the “Limited Population Pathway” allows the FDA to lower the evidence threshold required for the approval of certain antibiotics and antifungals, so long as they treat serious or life-threatening infections and address unmet medical needs.¹³⁹ The pathway anticipates approval based on non-traditional efficacy measures drawn from small studies as well as “(1) preclinical, pharmacologic, or pathophysiologic evidence; (2) nonclinical susceptibility and pharmacokinetic data; (3) data from phase 2 clinical trials; and (4) and such other confirmatory evidence as the Secretary determines appropriate to approve the drug.”¹⁴⁰ Antimicrobials approved in this manner would have disclaimers on their labeling indicating use for a limited population of patients. The pathway raises concerns insofar as it lowers evidentiary standards for approval, does not require that the drug be studied in patients with antibiotic-resistant infections, and does not provide adequate safeguards to limit use outside of the approved population.¹⁴¹

Finally, priority review vouchers were proposed in 2006 to provide incentives for manufacturers that obtain approval for drugs to treat qualifying neglected tropical diseases.¹⁴² The program now includes rare pediatric diseases (as of 2012)¹⁴³ and was further expanded to medical countermeasures via the 21st Century Cures Act.¹⁴⁴ Once a qualifying drug is approved, a

137. Hans-Georg Eichler et al., *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 426, 428 (2012).

138. EUR. MEDICINES AGENCY, FINAL REPORT ON THE ADAPTIVE PATHWAYS PILOT 2 (2016).

139. Michael S. Sinha & Aaron S. Kesselheim, *Regulatory Incentives for Antibiotic Drug Development: A Review of Recent Proposals*, 24 BIOORGANIC & MED. CHEMISTRY 6446, 6447 (2016).

140. Jerry Avorn & Aaron S. Kesselheim, *The 21st Century Cures Act: Will It Take Us Back in Time?* 372 NEW ENG. J. MED. 2473, 2474 (2015).

141. Sinha & Kesselheim, *supra* note 139, at 6449.

142. David B. Ridley et al., *Developing Drugs for Developing Countries*, 25 HEALTH AFF. 313, 313-14 (2006).

143. GAO, RARE DISEASES: TOO EARLY TO GAUGE EFFECTIVENESS OF FDA’S PEDIATRIC VOUCHER PROGRAM I (2016).

144. Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112-144, 126 Stat. 993 (2012); Michael S. Sinha et al., *Expansion of the Priority Review*

voucher is awarded that can either be sold to another drug manufacturer or used to obtain priority review of another drug made by that manufacturer. Advocates argue that priority review vouchers (both in terms of resale and redemption value) provide companies with greater incentive to invest in otherwise less lucrative areas of research and development.¹⁴⁵ Though some issued vouchers have sold for between \$67 million and \$350 million, multiple studies suggest that the program has failed in achieving its primary objective.¹⁴⁶ For example, a recent study evaluating the program's impact on stimulating research and development on neglected tropical diseases found a steady decrease in Phase I clinical trials from 2000 to 2014, with no impact observed of the 2007 legislation.¹⁴⁷ A study of the voucher program expansion under the 21st Century Cures Act to include medical countermeasures found that the majority of such drugs are developed with public funding, with little increase in research and development after the implementation of the incentive.¹⁴⁸ Finally, a study of the priority review voucher for rare pediatric diseases found no change in the rate of new pediatric drugs starting or completing clinical testing.¹⁴⁹ These studies have led some to question the utility of the priority review voucher program more generally,¹⁵⁰ with some FDA officials suggesting that priority review voucher programs be eliminated altogether because they increase the burden on the FDA without evidence of public health benefits.¹⁵¹

Voucher Program Under the 21st Century Cures Act: Implications for Innovation and Public Health, 44 AM. J. L. MED. 329, 332 (2018).

145. David B. Ridley & Stephane A. Régnier, *The Commercial Market for Priority Review Vouchers*, 35 HEALTH AFF. 776, 777 (2016).

146. Ameet Sarpatwari & Aaron S. Kesselheim, *Efficacy of the Priority Review Voucher Program*, 315 J. AM. MED. ASS'N. 1660, 1660 (2016).

147. Nina Jain et al., *Association of the Priority Review Voucher with Neglected Tropical Disease Drug and Vaccine Development*, 318 J. AM. MED. ASS'N 388-89 (2017).

148. Michael S. Sinha et al., *Expansion of the Priority Review Voucher Program Under the 21st Century Cures Act: Implications for Innovation and Public Health*, 44 AM. J. LAW & MED. 329, 341 (2018).

149. Thomas J. Hwang et al., *Impact of the Priority Review Voucher Program on Drug Development for Rare Pediatric Diseases*, 38 HEALTH AFF. 313, 317 (2019).

150. See e.g., Helen Branswell, *How a System Meant to Develop Drugs for Rare Diseases Broke Down*, STAT (Nov. 28, 2015), <https://www.statnews.com/2015/11/28/priority-review-vouchers-rare-diseases>.

151. Ed Silverman, *FDA Wants to Nix Voucher Program for Rare Pediatric Disease Drugs*, STAT (Mar. 3, 2016), <https://www.statnews.com/pharmalot/2016/03/03/fda-pediatric-disease-gao>.

F. *Expanded Access and Right-to-Try*

Patients generally cannot access an investigational drug outside of a clinical trial prior until it has been approved by the FDA¹⁵² but during that time period, an “expanded access protocol” permits some patients to access the drug via a request to the FDA.¹⁵³ Requesting access to an unapproved prescription drug outside the formal clinical trial setting is also known as “compassionate use,” and FDA receipt of such requests is increasing.¹⁵⁴ The three general categories of expanded access protocols pertain to the number of patients each affects: individuals, small groups, and large groups. Individual requests—the most common type—entails a physician making a special request to the FDA for a specific patient to be granted access to an investigational drug, such as under emergency circumstances.¹⁵⁵ In the second category of expanded access protocol, intermediate-size groups of patients (in the tens to hundreds) who are similar in some way request early access to a developmental drug.¹⁵⁶ The third category covers widespread use by large numbers of patients, and may occur after completion of a successful trial for an experimental agent, but prior to FDA approval and marketing.¹⁵⁷

The FDA must, on a case-by-case basis, rule that the condition is “serious or immediately life-threatening,” that “no comparable or satisfactory alternative therap[ies,]” exists, and that expanded access will not disrupt ongoing clinical trials.¹⁵⁸ The FDA allows companies to bill insurance companies for direct costs associated with expanded access, though most manufacturers end up providing the drug free of charge. To date, the agency has granted nearly every expanded access request, irrespective of category.¹⁵⁹

However, expanded access is unevenly available. Manufacturers vary in their willingness to support expanded access programs, as their priority is to successfully complete clinical trials and secure FDA approval.¹⁶⁰ One concern

152. *United States v. Rutherford*, 442 U.S. 544, 552 (1979); *Abigail Alliance v. von Eschenbach*, 495 F.3d 695, 697 (D.C. Cir. 2007).

153. *Expanded Access to Unapproved Therapies and Diagnostics*, 21 U.S.C. § 360b (2007).

154. Eline M. Bunnik et al., *The Changing Landscape of Expanded Access to Investigational Drugs for Patients with Unmet Medical Needs: Ethical Implications*, J. PHARMACEUTICAL POL'Y. & PRAC. 1, 1 (2017).

155. *Individual Patients, Including for Emergency Use*, 21 C.F.R. § 312.310 (2018).

156. *Intermediate-size Patient Populations*, 21 C.F.R. § 312.315 (2018).

157. *Treatment IND or Treatment Protocol*, 21 C.F.R. § 312.320 (2018).

158. *Requirements for All Expanded Access Uses*, 21 C.F.R. § 312.305 (2018).

159. Aaron S. Kesselheim et al., *Existing FDA Pathways Have Potential to Ensure Early Access to, and Appropriate Use of, Specialty Drugs*, 33 HEALTH AFF. 1770, 1771 (2014).

160. Elena Fountzilas et al., *Expanded Access to Investigational Drugs: Balancing Patient Safety with Potential Therapeutic Benefits*, 27 EXPERT OPINION INVESTIGATIONAL DRUGS 155, 157 (2018).

is that bad outcomes might jeopardize a drug's main application. While the manufacturer is often the main bottleneck to expanded access, physicians may not know expanded access options exist or may not want to take on the responsibility of making the request.¹⁶¹ The FDA has proposed paperwork said to require only forty-five minutes for physicians to complete.¹⁶²

In spite of this, some libertarian activists and allied patient groups argued the FDA process was too bureaucratic and began advocating for the option to request experimental therapeutics directly from the pharmaceutical manufacturer. The Colorado legislature passed the first "right-to-try" law in 2014; after that, at least thirty-six other states have passed similar laws, permitting manufacturers to provide terminally-ill patients with experimental medicines without the FDA's authorization.¹⁶³ On the federal level, Congress followed up by passing its own Right-to-Try Act in May 2018.¹⁶⁴ Lawmakers sought to prohibit regulatory agencies from considering outcomes from right-to-try when making regulatory decisions about an experimental drug, including whether or not it should be approved.¹⁶⁵ Shortly after its passage, the bill's primary sponsor, Senator Ron Johnson (R-WI), noted in a letter to the FDA Commissioner: "[the 'right-to-try' law] intends to diminish the FDA's power over people's lives, not increase it."¹⁶⁶ One recent report suggests the law has yet to be successful in achieving its aims.¹⁶⁷

161. See Alison Bateman-House, *How a Physician Can Work With a Not Yet Approved Drug Through Compassionate Use*, HEALTH CARE BLOG (Apr. 17, 2016), <http://thehealthcareblog.com/blog/2016/04/17/far-from-evidence-based-prescribing-the-world-of-compassionate-use>.

162. FDA, INDIVIDUAL PATIENT EXPANDED ACCESS APPLICATIONS: FORM FDA 3926 GUIDANCE FOR INDUSTRY 7 (2017).

163. Alison Bateman-House & Ameet Sarpatwari, *Don't Limit The Powers of the FDA*, BOS. GLOBE (Jul. 27, 2017), <https://www.bostonglobe.com/opinion/2017/07/26/don-limit-powers-fda/liKyNysP72ouOWinuwlOyI/story.html>; see RIGHT TO TRY IN YOUR STATE, <http://righttotry.org/in-your-state> (last visited Mar. 31, 2019).

164. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act, Pub. L. 115-176, § 204, 132 Stat. 1372 (2018) (codified at 21 U.S.C. § 360bbb).

165. Right to Try Act of 2017, H.R. 878, 115th Cong. § 2(b)(2) (2017) ("[T]he outcome of any production, manufacture, distribution, prescribing, dispensing, possession, or use of an experimental drug, biological product or device . . . shall not be used by a Federal agency reviewing the experimental drug, biological product, or device to delay or otherwise adversely impact review or approval of such experimental drug, biological product, or device.").

166. Erin Mershon, *"Right-to-Try" Law Intended to Weaken the FDA, Measure's Sponsor Says in Blunt Remarks*, STAT (May 31, 2018), <https://www.statnews.com/2018/05/31/right-to-try-ron-johnson>.

167. Nicholas Florko, *A Year After Trump Touted 'Right To Try,' Patients Still Aren't Getting Treatment*, STAT (Jan. 29, 2019), <https://www.statnews.com/2019/01/29/right-to-try-patients-still-arent-getting-treatment>.

G. Labeling

At the time an NDA is approved, the FDA also approves the product's labeling. Written by the manufacturer, the drug label includes key information about a drug and is intended to inform physicians how to use a given medication.¹⁶⁸ Labeling also includes a section for patients describing a drug's actions, possible side effects, and warnings. Additional leaflets may be handed out at the pharmacy level, although they vary in quality and utility and lack standardization or regulatory quality control.¹⁶⁹ Many physicians do not read the drug labeling before prescribing medications,¹⁷⁰ and the document itself includes so much information that it can be difficult for patients to determine which information is relevant.¹⁷¹

III. POST-APPROVAL DRUG POLICY ISSUES

A. Market Exclusivity

Once the FDA approves an investigational drug, the drug's manufacturer can count on a competition-free period of brand-name market exclusivity enforced by various laws.¹⁷² The Hatch-Waxman Act of 1983 guaranteed all new small molecule drugs five years before a generic drug manufacturer can submit an Abbreviated New Drug Application (ANDA).¹⁷³ Because ANDAs take about one to two years to approve, this means that most new drugs get a guaranteed six to seven year period of exclusivity.¹⁷⁴ The FDA Safety and Innovation Act of 2012 granted certain new antibiotic drugs five additional

168. Food & Drug Administration Labeling, 21 C.F.R. § 201 (2018).

169. Aaron S. Kesselheim et al., *Speaking The Same Language?: International Variations in the Safety Information Accompanying Top-Selling Prescription Drugs*, 22 BRIT. MED. J. QUALITY & SAFETY 727, 727-34 (2013).

170. This has often been noted in physician depositions. See e.g., *Bartlett v. Mut. Pharm. Co.*, 731 F. Supp. 2d 135, 143 (D. N.H. 2010) (“[Defendant physician] admitted at his deposition that he never reviewed Mutual’s Sulindac label before treating [plaintiff] and that “nothing about it influenced [his] prescribing of the drug” or what he told [plaintiff] about it. When asked if he reviewed the identical Clinoril label before treating [plaintiff], [defendant] responded “not in detail, no.” He then admitted that he never read the part of the Clinoril label that listed SJS/TEN as potential adverse reactions, nor the part that warned of “hypersensitivity” and “severe skin reactions” that have caused fatalities.”).

171. William H. Shrank & Jerry Avorn, *Educating Patients About Their Medications: The Potential and Limitations of Written Drug Information*, 26 HEALTH AFF. 736, 731-40 (2007).

172. Aaron S. Kesselheim et al., *Determinants of Market Exclusivity for Prescription Drugs in the United States*, 177 J. AM. MED. ASS’N INTERNAL MED. 1660, 1658-64 (2017).

173. Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 301 (1984).

174. Aaron S. Kesselheim et al., *Determinants of Market Exclusivity for Prescription Drugs in the United States*, 177 J. AM. MED. ASS’N INTERNAL MED. 1659, 1658-64 (2017).

years of generic-free exclusivity, for a total of about eleven to twelve years. Drugs for rare diseases designated by the Orphan Drug Act receive an exclusivity period of seven years after regulatory approval.¹⁷⁵ Although this form of market exclusivity cannot be challenged by a generic manufacturer, it also only applies to the approved indication—it does not apply to other uses of the same drug.¹⁷⁶ As a result, another manufacturer could technically develop the same active ingredient for a different clinical use and receive FDA approval without much of a problem, although this has rarely happened in reality. Finally, the 2009 Biologics Price Competition and Innovation Act (BPCIA) granted innovator manufacturers of biologic drugs a guaranteed minimum twelve-year period of exclusivity.¹⁷⁷ The twelve-year term was derived from industry-funded studies on the length of time it takes innovator manufacturers to recoup their investment.¹⁷⁸ Since then, the length of the exclusivity period has since been called into question; some legislators have pushed for the period to be reduced to seven years,¹⁷⁹ while another industry-sponsored bill sought to increase the term of some biologics to fifteen years.¹⁸⁰

Nearly all brand-name drugs have patent protections at the time of approval that often determines the duration of market exclusivity.¹⁸¹ Patents provide twenty years of exclusivity from the date of patent application filing.¹⁸² The earliest patents on a new drug, particularly those on the structure of the underlying active ingredient, must be sought around the time of the drug's discovery and will therefore provide less than twenty years of functional market exclusivity by the time the drug receives FDA approval; pre-approval testing may take six to ten years.¹⁸³

Patent term restoration is a process by which the FDA restores patent time lost to regulatory review for a period of up to five years, with a maximum cap of fourteen years on patent exclusivity for the primary patent.¹⁸⁴ A recent study looking at patent term restoration for eighty-three top-selling medicines found a median of 2.75 years added via patent term restoration, with three-quarters of

175. Protection for Drugs for Rare Diseases or Conditions, 21 U.S.C. § 360cc (2019).

176. Timothy Cote et al., *Orphan Products: An Emerging Trend in Drug Approvals*, 9 NATURE REV. DRUG DISCOVERY 1, 1-2 (2010).

177. Biologics Price Competition and Innovation Act of 2009, 126 Stat. 993 (2009).

178. See Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479, 486 (2008).

179. Price Relief, Innovation, and Competition for Essential Drugs of 2018 Act, H.R. 5573, 114th Cong. § 2(a) (2016).

180. Dormant Therapies Act of 2014, S. 3004, 113th Cong. § 3(1)(B) (2014).

181. Aaron S. Kesselheim et al., *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 J. AM. MED. ASS'N 861, 858-71 (2016).

182. Contents and Term of Patent; Provisional Rights, 35 U.S.C. § 154(a)(2) (2018).

183. Aaron S. Kesselheim et al., *Determinants of Market Exclusivity for Prescription Drugs in the United States*, 177 J. AM. MED. ASS'N 1659, 1658-64 (2017).

184. Extension of Patent Term, 35 U.S.C. § 156 (2015).

the sample reaching the patent term restoration limit of fourteen years.¹⁸⁵ Interestingly, in the median market exclusivity studies for first-in-class drugs and drugs with priority review, orphan, accelerated approval, and fast track designations, all had median market exclusivity periods of greater than fourteen years.¹⁸⁶

Drug manufacturers also seek multiple additional patents (so-called secondary patents) that can further extend market exclusivity by impeding or delaying generic entry.¹⁸⁷ The duration of market exclusivity can therefore vary depending on the product's current patent portfolio.¹⁸⁸ One study of widely-used drugs approved between 2000 and 2012 identified a median exclusivity period of 12.5 years;¹⁸⁹ other studies have found similar durations.¹⁹⁰

B. *Post-Approval Safety Surveillance*

After a prescription drug is approved, regulators, physicians, and patients continue to learn about its effectiveness and safety as part of the post-approval surveillance process. The FDA has a central role in monitoring during this time, but it is the primary responsibility of brand-name manufacturers to actively pursue emerging safety signals about their drugs and update the warnings included in the drug's labeling accordingly, as well as to alert consumers to newly-discovered risks associated with their drugs.¹⁹¹

The FDA's Adverse Event Reporting System (FAERS) is its primary mechanism of safety surveillance, collecting voluntary and user-generated reports about drugs from hospitals, healthcare professionals, and consumers.¹⁹² However, under-reporting is a substantial limitation—many physicians and patients may not know that an adverse outcome is due to a drug, and when they do, often do not think to report that outcome to the FDA or the

185. Reed F. Beall et al., *Patent Term Restoration for Top-Selling Drugs in the United States*, 24 *DRUG DISCOVERY TODAY* 21, 20-25 (2018).

186. Bo Wang et al., *Variations in Time of Market Exclusivity Among Top-Selling Prescription Drugs in the United States*, 175 *J. AM. MED. ASS'N* 635, 635-37 (2015).

187. Kerstin Noëlle Vokinger et al., *Strategies That Delay Market Entry of Generic Drugs*, 177 *J. AM. MED. ASS'N* 1666, 1665-69 (2017).

188. Reed F. Beall et al., *A Method for Approximating Future Entry of Generic Drugs*, 21 *VALUE IN HEALTH* 1382, 1382-89 (2018).

189. Wang, *supra* note 186, at 635-37.

190. Henry Grabowski et al., *Updated Trends in U.S. Brand-Name and Generic Drug Competition*, 19 *J. MED. ECON.* 1, 1-2 (2016); C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, Patent Challenges, and Effective Market Life In Pharmaceuticals*, 31 *J. HEALTH ECON.* 327, 337 (2012).

191. *Wyeth v. Levine*, 555 U.S. 555, 579 (2009); Postmarketing Reporting of Adverse Drug Experiences 21 C.F.R. § 314.80(c).

192. FDA, *QUESTIONS AND ANSWERS ON FDA'S ADVERSE EVENT REPORTING SYSTEM (FAERS)* (June 4, 2018), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

manufacturer.¹⁹³ FAERS data are publicly available and updated four times a year; however, the data are not easy to access or interpret in part because there are no denominators of all patients taking the drug without incident. The data are also difficult to validate, and data entries are often incomplete.¹⁹⁴

Phase IV clinical studies are more formal evaluations of the long-term effects of drugs approved by the FDA. Manufacturers will often agree to these post-approval studies at the time of approval, but many are delayed beyond the agreed-to date of completion or not completed at all.¹⁹⁵ By the early 2000s, twice as many new drugs (about 80%) were subjected to post-approval study requests or requirements compared to the late 1970s (36%).¹⁹⁶ But the FDA possesses limited power to mandate timely completion of confirmatory post-approval trials. Of the Phase IV studies requested by the FDA for the twenty new drugs approved in 2008, 60% had not been completed four years later.¹⁹⁷ The study also highlighted the importance of Phase IV studies in generating new safety data about approved drugs: boxed safety warnings (5, 25%) and standard warnings or precautions (4, 20%) were added to about half the drugs in the cohort.¹⁹⁸

In the 2007 FDA Amendments Act,¹⁹⁹ Congress strengthened the FDA's post-approval oversight authority in 2007 in a variety of ways, responding to the FDA's inability to act on emerging reports about the elevated risk of heart attack and stroke associated with rofecoxib (Vioxx), even after five years on the market.²⁰⁰ One was to enable the FDA to seek civil monetary penalties from manufacturers for non-compliance.²⁰¹ However, the FDA remains reluctant to take remedial action when confirmatory trials are not completed in a timely manner (fines have never been invoked due to administrative complexity).²⁰² Another of those new powers was to create the Sentinel

193. Postmarketing Reporting of Adverse Drug Experiences, *supra* note 191.

194. FDA, QUESTIONS AND ANSWERS ON FDA'S ADVERSE EVENT REPORTING SYSTEM (FAERS) (last visited May 14, 2019), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

195. Thomas J. Moore & Curt D. Furberg, *Development Times, Clinical Testing, Postmarket Follow-Up, and Safety Risks for the New Drugs Approved by the US Food and Drug Administration: The Class of 2008*, 174 J. AM. MED. ASS'N 90, 94 (2014).

196. Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule*, 61 FOOD & DRUG L. J. 295, 304, 328 (2006).

197. Moore & Furberg, *supra* note 195, at 90, 94.

198. *Id.*

199. Food & Drug Administration Amendment Act of 2007, 121 Stat. § 823 (2007).

200. Debabrata Mukherjee et al., *Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors*, 286 J. AM. MED. ASS'N 954, 954 (2001).

201. Zachary Brennan, *Tracking FDAAA Noncompliance: AllTrials Calls on FDA to Levy Fines*, Regulatory Focus (Feb. 19, 2018), <https://www.raps.org/news-and-articles/news-articles/2018/2/tracking-fdaaa-noncompliance-alltrials-calls-on-f>.

202. Moore & Furberg, *supra* note 195, at 94; *see also* FDA, GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND CLINICAL TRIALS—IMPLEMENTATION OF SECTION 505(O)(3) OF

program, a collaboration between the FDA and seventeen national data partners focused on post-market safety surveillance of approved drugs.²⁰³ Sentinel is a distributed data network of over 100 million patients.²⁰⁴ Data from the Sentinel program are not collected in a central computer repository but instead held by participating commercial insurance companies in a standard format that can be tapped and mined as necessary. The FDA also has access to government insurance program datasets, via the Centers for Medicare and Medicaid Services, Veterans Affairs, and the Department of Defense, to utilize for safety surveillance.²⁰⁵ The agency is still working through procedures for using these datasets, and questions still remain with regard to access to this information for outside drug safety research.²⁰⁶ However, one study comparing Sentinel to a protocol-driven assessment found roughly equivalent hazard ratios of adverse events related to angioedema in patients taking angiotensin-converting enzyme inhibitors versus beta-blockers.²⁰⁷

Observational studies using large databases outside of the Sentinel system to assess emerging safety signals about prescriptions are conducted by pharmaceutical manufacturers and in academic research settings. Results from these studies may influence the FDA to change safety warnings about approved drugs.²⁰⁸ This work can be enhanced by data sharing—larger data sets with more variables and an enhanced ability to sort by outcome or exposure—though researchers need to be cognizant of limits placed on data sharing under the Health Insurance Portability and Accountability Act of 1996.²⁰⁹ In addition, some states have set up all-payer claims databases to collect medical and pharmacy claims from public and private payers and offer a comprehensive

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 1 (2016), <https://www.fda.gov/media/116878/download>.

203. FDA'S SENTINEL INITIATIVE, FDA (May 5, 2018), <https://www.fda.gov/safety/fdas-sentinel-initiative>.

204. FDA'S SENTINEL INITIATIVE: BACKGROUND, FDA (Nov. 17, 2017), <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm>.

205. FDA, ADVANCES IN FDA'S SAFETY PROGRAM FOR MARKETED DRUGS: ESTABLISHING PREMARKET SAFETY REVIEW AND MARKETED DRUG SAFETY AS EQUAL PRIORITIES AT FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH 11, 17 (2012), <https://www.fda.gov/downloads/Drugs/DrugSafety/UCM300946.pdf>.

206. Richard Platt et al., *The U.S. Food and Drug Administration's Mini-Sentinel Program: Status and Direction*, 21 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1, 7 (2012).

207. Joshua J. Gagne et al., *Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association*, 100 CLINICAL PHARMACOLOGY & THERAPEUTICS 558, 558 (2016).

208. See Jessica M. Franklin et al., *Evaluating the Use of Nonrandomized Real World Data Analyses for Regulatory Decision Making*, CLINICAL PHARMACOLOGY & THERAPEUTICS 1, 9 (2019).

209. See Ameet Sarpatwari, *Ensuring Patient Privacy in Data Sharing for Postapproval Research*, 371 NEW ENG. J. MED. 1644, 1644 (2014).

view of patient interactions with the health care system.²¹⁰ They can be a very valuable tool for evaluating drug safety, effectiveness, and costs, but their existence is under threat. In *Gobeille v. Liberty Mutual*,²¹¹ self-insured plans claimed that the Employee Retirement Income Security Act of 1974 prevents states from compelling them to report data; the Supreme Court agreed, dealing a blow to the viability of all-payer claims databases.²¹² After this ruling, some large health insurers have continued to provide claims data on a voluntary basis.²¹³

Historically, the FDA has been able to require risk management plans for drugs with well-known safety risks. For example, the acne drug isotretinoin (Accutane) posed very high teratogenic potential, so the FDA required a negative pregnancy test and heightened informed consent requirements, including the recommendation that women take two different forms of birth control to accompany each prescription.²¹⁴ In 2007, the authority to require such heightened steps for prescribing was codified with the creation of the risk evaluation and mitigation strategy (REMS) program.²¹⁵ For drugs with the most serious safety concerns, the FDA can direct the manufacturer to more closely monitor patients, mandate training and certification for prescribers, and place various restrictions on dispensing.²¹⁶ Though REMS are explicitly required not to place undue burden on patient access and to minimize burden to the health care delivery system,²¹⁷ there is concern that certain REMS requirements may be overly onerous for prescribers and manufacturers, cutting into sales volume by limiting prescribing and dispensing practices.²¹⁸ With implicit authorization from the FDA, some manufacturers have patented their REMS, undermining potential generic competition and leading to extensions in

210. Michael Dworsky, *Using All-Payer Claims Databases to Study Insurance and Health Care Utilization Dynamics*, 32 J. GEN. INTERNAL MED. 1069, 1069-70 (2017).

211. 136 S. Ct. 936 (2016).

212. Sean E. Bland et al., *Strategies for Health System Innovation After Gobeille v. Liberty Mutual Insurance Company*, 316 J. AM. MED. ASS'N 581, 581-82 (2016); Erin F. Brown & Jaime King, *The Consequences Of Gobeille v. Liberty Mutual For Health Care Cost Control*, HEALTH AFF. BLOG (Mar. 10, 2016).

213. John D. Freedman et al., *All-Payer Claims Databases: Uses and Expanded Prospects after Gobeille*, 375 NEW ENG. J. MED. 2215, 2217 (2016).

214. See generally THE IPLEDGE PROGRAM: PRESCRIBER ISTOTRETINOIN EDUCATIONAL KIT (2013), <https://www.ipledgeprogram.com/iPledgeUI/remis/pdf/resources/Prescriber%20Isotretinoin%20Educational%20Kit.pdf>.

215. RISK EVALUATION AND MITIGATION STRATEGIES (REMS), FDA (Feb. 2, 2018), <https://www.fda.gov/Drugs/DrugSafety/REMS/default.htm>.

216. *Id.*

217. Risk Evaluation and Mitigation Strategies, 21 U.S.C. § 355-1(f).

218. See DEP'T OF HEALTH & HUM. SERVS., FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY (2013), <https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf> (noting concerns that the FDA has had difficulty collecting information from third parties to measure risk evaluation and mitigation strategies).

market exclusivity.²¹⁹ This has led to questions about how to handle REMS when generic versions of the drug can be made available, since the most efficient system would be for the brand-name and generic manufacturers to use the same REMS system.²²⁰ Recently proposed legislation would eliminate this confusion by permitting either an independent REMS or a single, shared REMS for newly-approved generic drugs.²²¹ Most recently, a study of REMS for opioid drugs criticized FDA oversight of those programs, which did not lead to a re-examination of the safety of the products even in light of evidence suggesting noncompliance with the REMS.²²²

After new approval, new knowledge about a marketed prescription drug may result in the addition of new warnings to a drug's labeling, including changes to dosing regimens, drug-drug interactions, and the most high-profile warning, a boxed warning.²²³ Brand-name manufacturers bear responsibility for the content of the labeling and can be the subject of product liability suits for failure to warn relating to drug labeling language that insufficiently communicates risk.²²⁴ There has been controversy as to how risks should be depicted on the FDA-approved label and which party is responsible for changing the language describing such risks, particularly after generic entry has occurred.²²⁵ As discussed below in more detail, the Supreme Court established that generic manufacturers are not liable for updating a drug's safety labeling.²²⁶

In 2007, the FDA was given heightened authority to require labeling changes "if the Secretary becomes aware of new information . . . that the Secretary believes should be included in the labeling of the drug."²²⁷ The drug

219. Michael A. Carrier & Brenna Sooy, *Five Solutions to the REMS Patent Problem*, 97 B.U. L. REV. 1661, 1662 (2017).

220. Ameet Sarpatwari et al., *Using a Drug-Safety Tool to Prevent Competition*, 370 NEW ENG. J. MED. 1476, 1476 (2014).

221. Creating and Restoring Equal Access to Equivalent Samples Act, S. 974, 115th Cong. (2017-18); Ameet Sarpatwari & Aaron S. Kesselheim, *Get Generic Drugs to Market Faster*, BLOOMBERG OPINION (June 20, 2017) <https://www.bloomberg.com/view/articles/2017-06-20/get-generic-drugs-to-market-faster>.

222. See Ameet Sarpatwari & Gregory Curfman, *Mitigating Health Risks of Prescription Drugs: Lessons From FDA Oversight of Opioid Products*, 321 J. AM. MED. ASS'N 651, 652 (2019); see generally Jeffrey E. Rollman et al., *Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products*, 321 J. AM. MED. ASS'N 676 (2019).

223. FDA, A GUIDE TO DRUG SAFETY TERMS AT FDA 2 (2012).

224. *Wyeth*, *supra* note 191, at 570-71.

225. See generally FOOD AND DRUG ADMIN. GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES: IMPLEMENTATION OF SECTION 505(O)(4) OF THE FD&C ACT (2013) (describing the process that the FDA must use to unilaterally make safety-related labeling changes based on new safety information that becomes available after approval of the drug or biological product).

226. *Pliva, Inc. v. Mensing*, 564 U.S. 604, 624 (2011).

227. 21 U.S.C. § 355(o)(4)(A).

safety communication is another mechanism by which the FDA alerts both physicians and patients as new safety data emerges pertaining to marketed prescription drugs.²²⁸ Since 2010, over 250 drug safety communications have been issued by the agency.²²⁹ A series of studies looking at the impact of drug safety communications related to zolpidem (Ambien) identified limited impact on prescribing patterns²³⁰ and inconsistent messaging across mainstream media²³¹ and social media platforms.²³² A third approach to drug safety messaging and dissemination, the FDA's MedWatch program, is a consumer-facing website and smartphone application that allows for simple queries of drug safety information and regulatory changes.²³³

The FDA also has the authority to require that an unsafe drug be withdrawn from the market, although in most cases the manufacturer voluntarily takes that step before the FDA acts.²³⁴ Safety-related market withdrawals are rare: only three drugs approved between 2001 and 2010 were withdrawn from the market.²³⁵ Market withdrawals and addition of boxed warnings are increasing over time.²³⁶ One study found that drugs approved after 1992 (post-PDUFA) were more likely to receive boxed warnings or be withdrawn from the market, as compared to pre-PDUFA approved drugs.²³⁷ A second study found that, of new drugs approved between 1980 and 2009, 16% were eventually withdrawn from the market, though safety was the primary documented reason for only one-quarter of those withdrawals.²³⁸

228. DRUG SAFETY COMMUNICATIONS, FDA (April 9, 2019), <http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>.

229. *Id.*

230. Aaron S. Kesselheim et al., *Changes in Prescribing and Healthcare Resource Utilization After FDA Drug Safety Communications Involving Zolpidem-Containing Medications*, 26 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 712, 716 (2017).

231. See Steve Woloshin et al., *Media Coverage of FDA Drug Safety Communications About Zolpidem: A Quantitative and Qualitative Analysis*, 22 J. HEALTH COMM. 365, 365 (2017).

232. Michael S. Sinha et al., *Social Media Impact of the Food and Drug Administration's Drug Safety Communication Messaging About Zolpidem: Mixed-Methods Analysis*, 4 JMIR PUB. HEALTH & SURVEILLANCE 1, 7 (2018).

233. *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, FOOD & DRUG ADMIN, <http://www.fda.gov/Safety/MedWatch> (last visited April 17, 2019).

234. Recall Policy, 21 C.F.R. § 7.40.

235. Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 J. AM. MED. ASS'N 1854, 1854 (2017).

236. Frank C. Himmelstein et al., *Era of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings and Market Withdrawals*, 33 HEALTH AFF. 1453, 1454 (2014).

237. *Id.* at 1456.

238. Zaina P. Qureshi et al., *Market Withdrawal of New Molecular Entities Approved in the United States From 1980 To 2009*, 20 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 772, 777 (2011).

C. Pricing of Patented Drugs

Once a drug is approved, the brand-name manufacturer sets its initial price in the United States at what the manufacturer estimates that the market will bear.²³⁹ This practice is distinct from that of other high-income countries, which to differing degrees have government-affiliated organizations that negotiate a price based on evaluation of the drug's clinical and cost-effectiveness. As a result, most brand-name drugs cost far more in the United States than in other comparable settings around the world. Another distinct feature of the U.S. market is that manufacturers tend to increase prices over time prior to expiration of market exclusivity even in the absence of new information about the drug's value.

In the United States, the primary counterweight against the price set by the manufacturer is the negotiating power of the payor. Among public payors, the Centers for Medicare and Medicaid Services (CMS) is responsible for the bulk of federal coverage for prescription drugs. Medicare covers about sixty million adults for their outpatient (Part D) and inpatient (Parts A and B) prescriptions, with forty-three million enrolled in Part D plans.²⁴⁰ Medicaid, the insurance program for the poor, is jointly funded by federal and state governments and covers prescription drugs for nearly seventy-three million Americans.²⁴¹ Both programs have a complex and non-transparent system by which they receive rebates from manufacturers that lower costs to the federal government.²⁴² In spite of these discounts, costs continue to rise: Medicare Part D costs are estimated to approach \$100 billion in 2019.²⁴³

The Medicare Part D-eligible population consists of people aged sixty-five and older, those with end-stage renal disease, and those with total and permanent disability. The outpatient benefit is offered through individual plans, but Medicare Part D legislation forbids CMS from negotiating prices, or otherwise interfering with negotiations between Part D plan administrators and pharmaceutical companies.²⁴⁴ This policy was based on the presumption that

239. Kesselheim, *supra* note 178, at 858.

240. AN OVERVIEW OF THE MEDICARE PART D PRESCRIPTION DRUG BENEFIT, KAISER FAM. FOUND. (Oct. 12, 2018), <https://www.kff.org/medicare/fact-sheet/an-overview-of-the-medicare-part-d-prescription-drug-benefit>.

241. Total Monthly Medicaid and CHIP Enrollment, KAISER FAM. FOUND., <https://www.kff.org/health-reform/state-indicator/total-monthly-medicare-and-chip-enrollment> (navigate to "Dec. 2018" in the "Timeframe" drop-down menu) (last visited Apr. 17, 2019).

242. *See e.g.*, 42 U.S.C. § 1396r-8(c) (2019) (discussing calculation of rebates for the Medicaid program). A few prices are not factored into the Medicaid pricing system, such as the price offered to the Veterans Affairs health system. For more, see Brett Venker et al., *Assessment of Spending in Medicare Part D If Medication Prices from the Department of Veterans Affairs Were Used*, 179 J. AM. MED. ASS'N INTERNAL MED. 431, 431 (2019).

243. 42 U.S.C. § 1396r-8(k)(2) (2019); KAISER FAM. FOUND., *supra* note 240.

244. 42 U.S.C. § 1395w-111(i) (2010).

government negotiating leverage would lead to substantially reduced revenues for the pharmaceutical industry.²⁴⁵ There are also formulary restrictions such as the requirement that at least one drug be covered in each class and six special protected drug classes for which essentially all FDA-approved drugs must be covered, such as cancer and psychiatric drugs, further limiting Medicare Part D payors' ability to curb program costs.²⁴⁶

Individual states can negotiate additional discounts within the Medicaid program, but are limited by legal mandates to cover essentially all FDA-approved drugs, even those that may offer poor value.²⁴⁷ Medicaid programs may, however, impose obstacles to access such as prior authorization (in which a provider has to get special approval to prescribe a drug) or step-therapy approaches (in which patients must try and fail cheaper alternatives before pricier brand-name drugs are approved by insurers).²⁴⁸ With increasing proportions of state Medicaid budgets going to prescription drugs, some states have been forced to cut back on other services or tighten eligibility requirements. In the first few years after the hepatitis C treatment sofosbuvir (Sovaldi) was approved, several state Medicaid programs restricted access to the drug on the basis of non-evidence-based policies, including denying coverage to active drug or alcohol users.²⁴⁹ In response, some states have pursued creative measures to ensure access; for instance, Louisiana has tried to negotiate terms of a subscription service model for hepatitis C drugs with manufacturer Gilead.²⁵⁰

Other public payors include Veterans Affairs, state prisons, and Federal Employees Health Benefits Program. The Veterans Affairs system gets an automatic statutorily guaranteed rebate, but also has flexibility to exclude particular drugs from its formulary and negotiates on behalf of the veterans it covers, two factors that allow it to get the best prices among public payors—particularly for newly-approved brand-name drugs.²⁵¹ Still, these systems are struggling with increasing drug costs in recent years. For example, the high costs of sofosbuvir and ledipasvir/sofosbuvir (Harvoni) imposed problems for health budgets for departments of correction, where hepatitis C infection is

245. See generally Kevin Outterson & Aaron S. Kesselheim, *How Medicare Could Get Better Prices On Prescription Drugs*, 28 HEALTH AFF. 832 (2009).

246. 42 U.S.C. § 1396r-8(k)(2); KAISER FAM. FOUND., *supra* note 240.

247. See Benjamin D. Sommers & Aaron S. Kesselheim, *Massachusetts' Proposed Medicaid Reforms—Cheaper Drugs and Better Coverage?* 378 NEW ENG. J. MED. 109, 111 (2018).

248. 42 U.S.C. § 1396r-8(d)(1).

249. See Amy Kapczynski & Aaron S. Kesselheim, *Government Patent Use: A Legal Approach to Reducing Drug Spending*, 35 HEALTH AFF. 791, 791, 794-95 (2016).

250. Melinda Deslatte, *Louisiana Seeking 'Subscription Model' For Hepatitis C Drugs*, ASSOCIATED PRESS (Sept. 21, 2018), <https://www.apnews.com/50d4713d213640318d71b12c5173f41a>.

251. Limitation on Prices of Drugs Procured by Department and Certain Other Federal Agencies, 38 U.S.C. § 8126.

common.²⁵² In response, these payors have employed restrictions such as prior authorization and step therapy.²⁵³

A federal law—codified at 21 U.S.C. § 1498—permits governmental use of patented inventions without permission, so long as “reasonable and entire compensation” is provided to the patent holder.²⁵⁴ Through this process, patients in federal programs could receive medications while still allowing companies to be rewarded for investments in research and development. This could potentially save the government millions of dollars compared to what it currently pays, depending on how “reasonable and entire compensation” is applied. In recent decades, the government has invoked this power only once in the pharmaceutical context, during the anthrax scare of 2001 when it sought to stockpile the antibiotic ciprofloxacin (Cipro) in case of widespread need against a bioterror attack and the manufacturer responded by cutting the price and increasing supply. Principled use of Section 1498 for highly expensive, essential medications could increase access and lower prices;²⁵⁵ for example, using this power for branded naloxone products could increase access during the opioid epidemic.²⁵⁶

Another potential pathway to intervene on excessive pricing of drugs with patents directly traceable to government grant funding relates back to Bayh-Dole.²⁵⁷ In allowing federal grantees to issue exclusive licenses for inventions made using government grant funding, the statute also provided the government with safeguards: a royalty-free license to use the invention and march-in rights that permit the federal government to intervene and re-license the invention to another entity. These march-in rights are meant to be invoked in four circumstances: (1) a pressing public health need; (2) a licensee that did not take reasonable efforts to make the invention available to the public; (3) a licensee that violated an agreement for public use of a government-funded invention; or (4) a licensee that violated an agreement to manufacture an invention in the United States.²⁵⁸ Though five march-in rights requests have

252. Tianhua He et al, *Prevention of Hepatitis C by Screening and Treatment in U.S. Prisons*, 164 ANNALS INTERNAL MED. 84, 84 (2016).

253. Peter Loftus & Gary Fields, *High Cost of New Hepatitis C Drugs Strains Prison Budgets, Locks Many Out of Cure*, WALL ST. J. (Sept. 12, 2016), <https://www.wsj.com/articles/high-cost-of-new-hepatitis-c-drugs-strains-prison-budgets-locks-many-out-of-cure-1473701644>.

254. 28 U.S.C. § 1498 (1998); Kapczynski & Kesselheim, *supra* note 249, at 793.

255. Memorandum from Joshua M. Sharfstein et al. to the Secretary of Health of Louisiana, (May 4, 2017); Sarah Jane Tribble, *Louisiana Proposes Tapping A Federal Law To Slash Hepatitis C Drug Prices*, KAISER HEALTH NEWS (May 4, 2017), <http://khn.org/news/louisiana-proposes-tapping-a-federal-law-to-slash-hepatitis-c-drug-prices>.

256. Alex Wang & Aaron S. Kesselheim, *Government Patent Use to Address the Rising Cost of Naloxone: 28 U.S.C. § 1498 and Evzio*, 46 J. L. MED. & ETHICS 472, 481 (2018).

257. *See generally* Alfred D. Engelberg & Aaron S. Kesselheim, *Use the Bayh-Dole Act to Lower Drug Prices for Government Healthcare Programs*, 22 NATURE MED. 576 (2016).

258. 35 U.S.C. § 203.

been publicly reviewed by NIH in the past 35 years, the authority has never been used in the context of prescription drugs.²⁵⁹ However, two of the five requests led to voluntary concessions from the manufacturer related to price and availability.

Another approach for a subset of health care facilities to save on drug costs is through the federal “340b” drug pricing program. Under 340b, drug companies must provide certain medications at substantial discounts to specially-designated pharmacies associated with certain health care systems. The statute originally required the 340b pharmacy to be housed within a nonprofit hospital or a federally qualified health center that meets statutorily-designated criteria regarding provided care to underserved populations. The savings are intended to help those facilities offset the cost of caring for those populations.²⁶⁰ The Affordable Care Act expanded the 340b program to cancer hospitals, which now allows those facilities to purchase oncologic drugs at discounted prices, coupled with higher rates of reimbursement, as compared to outpatient facilities.²⁶¹ Such arrangements have become an important revenue stream for many health care organizations, but have also come under fire from the pharmaceutical industry.²⁶² One study found that, in recent years, hospitals with 340b pharmacies were expanding their reach to more affluent populations with better insurance coverage at the expense of the vulnerable patient populations the law was designed to benefit.²⁶³ As a consequence, Congress has been actively debating the future of the program.²⁶⁴

Finally, private payors cover prescription drug benefits for about 175 million people in the United States,²⁶⁵ primarily through pharmaceutical benefits managers (PBMs), the largest three being Express Scripts, CVS Caremark, and United Healthcare. PBMs were expected to reduce drug costs—and costs to the health care system at large—by streamlining important

259. Carolyn L. Treasure et al., *Do March-In Rights Ensure Access to Medical Products Arising From Federally Funded Research? A Qualitative Study*, 93 MILBANK Q. 761, 776 (2015).

260. Veterans Health Care Act, 106 Stat. 4943 (1992).

261. Bo Wang et al., *Chemotherapy Parity Laws: A Remedy for High Drug Costs?*, 174 J. AM. MED. ASS'N INTERNAL MED. 1721, 1722 (2014).

262. OFFICE OF INSPECTOR GEN., PART B PAYMENTS FOR 340B-PURCHASED DRUGS (2015); see also MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: OVERVIEW OF THE 340B DRUG PRICING PROGRAM 2-3 (2015).

263. Rena M. Conti & Peter B. Bach, *The 340B Drug Discount Program: Hospitals Generate Profits By Expanding To Reach More Affluent Communities*, 33 HEALTH AFF. 1786, 1786 (2014).

264. See e.g., H.R. ENERGY AND COMMERCE COMM., 115TH CONG., REVIEW OF THE 340B DRUG PRICING PROGRAM 3 (2018) (reporting the result of a Congressional investigation finding, among other conclusions, that “Congress should clarify the intent of the program”).

265. E.J. Emanuel, *We Can't Afford The Drugs That Could Cure Cancer*, WALL ST. J. (Sept. 20, 2018), <https://www.wsj.com/articles/we-cant-afford-the-drugs-that-could-cure-cancer-1537457740>.

administrative aspects of drug delivery from pharmaceutical companies to patients.²⁶⁶ Some insurers and PBMs have in recent years succeeded in getting lower prices for some very costly drugs, either when the clinical outcomes have not yet been described (e.g., PCSK9 inhibitors for high cholesterol) or when there is some substitutability in the class (e.g., after the second and third direct-acting antiviral drugs for hepatitis C were approved).²⁶⁷ But in other cases, there are legal restrictions on private payors' ability to negotiate. For example, many states require private payors to cover non-FDA-approved (off-label) indications of cancer drugs, so long as the indications are listed in one of a few national compendia.²⁶⁸ In addition, aggressive price negotiation has been the exception rather than the rule among private payors because a substantial proportion of PBMs' annual fees are a proportion of a given payor's drug spending.²⁶⁹ PBMs have also become a target of Congressional investigations over high drug prices, related in part to horizontal consolidation in the PBM marketplace and the resulting growth in their bargaining power during price negotiations.²⁷⁰

A major issue related to a drug's price is how much of it a patient pays in out-of-pocket fees. A Gallup survey found that 13.7% of Americans were uninsured in late 2018, meaning that they also lacked prescription drug coverage and paid full retail price for drugs in the absence of cost assistance programs.²⁷¹ Though most patients have insurance, the extent of prescription drug coverage is variable; some insurance programs, like Medicaid, cover nearly all the cost of a drug, while high-deductible private plans will transfer much of the cost to the individual.²⁷² Other insurers and managed care organizations attempt to discourage use of high-cost drugs when less expensive

266. Stephan L. Burton et al., *The Ethics of Pharmaceutical Benefit Management*, 20 HEALTH AFF. 150, 153-56 (2001).

267. Steve Miller, *When PCSK9 Inhibitors Compete*, EXPRESS SCRIPTS (Aug. 27, 2015), <http://lab.express-scripts.com/lab/insights/drug-options/when-pcsk9-inhibitors-compete>.

268. Fabrice Smieliauskas et al., *State Insurance Mandates and Off-Label Use of Chemotherapy*, 27 HEALTH ECON. 56, 56 (2017); *ASCO Advocacy for Coverage of Off-Label Oncology Drug Uses*, 2 J. ONCOLOGY PRACTICE 225, 225 (2006).

269. PATRIA M. DANZON, 2014 ERISA ADVISORY COUNCIL: PBM COMPENSATION AND FEE DISCLOSURE 3, 11 (2014), <https://www.dol.gov/sites/default/files/ebsa/about-ebsa/about-us/erisa-advisory-council/2014-pbm-compensation-and-fee-disclosure-danzon-06-19.pdf>; Bill Alpert, *Pharmacy-Benefit Managers Under Pressure*, BARRON'S (July 23, 2016), <http://www.barrons.com/articles/pharmacy-benefit-managers-under-fire-1469247082>.

270. *The State of Competition in the Pharmacy Benefit Manager and Pharmacy Marketplaces: Hearing Before the H. Comm. on the Judiciary*, 114th Cong. 3, 56-57 (2015).

271. Dan Witters, *U.S. Uninsured Rate Rises to Four-Year High*, GALLUP (Jan. 23, 2019), <https://news.gallup.com/poll/246134/uninsured-rate-rises-four-year-high.aspx>.

272. Drew Armstrong & Caroline Chen, *Regeneron in Express Scripts' Sights for Price War*, BLOOMBERG (Jan. 13, 2015), <http://www.bloomberg.com/news/articles/2015-01-13/after-roiling-hepatitis-market-express-scripts-eyes-cholesterol>.

alternatives are available, often by requiring a high patient co-payment for the former and a lower co-payment for the latter.²⁷³

Manufacturers have responded by offering drug coupons and patient assistance programs²⁷⁴ to cover co-payments and other out-of-pocket costs, aimed at encouraging adherence by reducing consumer costs.²⁷⁵ Coupons may compensate patients for co-pay expenses but the insurer is still obliged to pay the remaining (much larger) proportion of a brand name drug's costs, resulting in increased utilization of more expensive medications, with higher costs to insurance companies, and eventually, higher premiums to patients.²⁷⁶ One comparative study found that coupons did not lower system costs and may have slowed transition from brand-name drugs to alternative generic therapies.²⁷⁷ In fact, some coupons have recommended that "patients who prefer brand-name medicine" request that providers "write 'brand medically necessary,' 'may not substitute,' or 'dispense as written' on the prescription."²⁷⁸ Finally, some pharmacies offer lower cash rates for generic pharmaceuticals when purchased outside of a patient's insurance plan, although these often have changing formularies.²⁷⁹

Cost-related nonadherence is increasingly common: 21% of responders to a 2017 poll reported that a family member experienced cost-related barriers when attempting to fill a prescription in the last year.²⁸⁰ Patients started on a brand-name version of a drug were found to have lower adherence rates than those started on a comparable generic drug.²⁸¹ In one study, initial prescription of a generic statin for hyperlipidemia resulted in an 8% decrease in composite endpoints of cardiovascular events and death as compared to a patient started

273. Dana P. Goldman et al., *Prescription Drug Cost Sharing: Associations with Medication and Medical Utilization and Spending and Health*, 298 J. AM. MED. ASS'N 61, 61 (2007).

274. David H. Howard, *Drug Companies' Patient-Assistance Programs—Helping Patients or Profits?*, 371 NEW ENG. J. MED. 97, 97 (2014).

275. Joseph Ross & Aaron S. Kesselheim, *Prescription-Drug Coupons: No Such Thing As A Free Lunch*, 369 NEW ENG. J. MED. 1188, 1188 (2013). Of note, coupons are not legal in government programs. Goldman et al., *supra* note 273, at 62.

276. Catherine I. Starner et al., *Specialty Drug Coupons Lower Out-Of-Pocket Costs and May Improve Adherence at the Risk of Increasing Premiums*, 33 HEALTH AFF. 1761, 1766 (2014).

277. Leemore S. Dafny et al., *Undermining Value-Based Purchasing: Lessons from the Pharmaceutical Industry*, 375 NEW ENG. J. MED. 2013, 2014 (2016).

278. *Why Nexium?*, ASTRAZENECA, <https://www.purplepill.com/heartburn-relief/generic-nexium.html> (last visited April 17, 2019).

279. Niteesh K. Choudhry & William H. Shrank, *Four-Dollar Generics: Increased Accessibility, Impaired Quality Assurance*, 363 NEW ENG. J. MED. 1885, 1885-86 (2010).

280. Bianca DiJulio et al., *Data Note: Americans' Challenges with Health Care Costs*, KAISER FAM. FOUND. (Mar. 2, 2017), <https://www.kff.org/health-costs/poll-finding/data-note-americans-challenges-with-health-care-costs>.

281. Josuhua J. Gagne et al., *Comparative Effectiveness of Generic and Brand-Name Statins on Patient Outcomes*, 161 ANNALS OF INTERNAL MED. 400, 405 (2014).

on a brand-name statin, likely mediated by reduced adherence.²⁸² Suboptimal disease management associated with nonadherence due to cost was estimated in 2013 to cost health systems \$105 billion annually.²⁸³

In recent years, Congress has debated proposals for controlling drug costs. Many have suggested lifting the ban on Medicare Part D's prohibition on negotiating drugs prices,²⁸⁴ but others question whether lifting the prohibition alone without a central Medicare Part D formulary will result in cost savings.²⁸⁵ Another suggestion is to allow dual-eligibles—patients who are eligible for both Medicare Part D and Medicaid—to switch back from Medicare Part D to Medicare prescription drug coverage;²⁸⁶ Medicare Part D coverage for dual-eligibles was part of the creation of Part D in 2006. There is real concern that such a proposal would place further strain on state budgets.

Congress has recently debated proposals for importing drugs from countries, such as Canada, that have cheaper pharmaceuticals due to price controls. The law currently forbids the practice, although the FDA makes exceptions for drugs not approved in the United States that are imported by individuals for their personal use.²⁸⁷ Others argue that importing from countries with drug price controls is a temporary fix that drug companies will work to undermine, raising questions about the sustainability of such a policy, as well as its long-term effects on global prices.²⁸⁸

One recent proposal from the current presidential administration was to shift some Medicare Part D drugs to Medicare Part B; an analysis of that proposal suggests that the shift may save costs, but that a minority of patients

282. *Id.*

283. IMS INST. FOR HEALTHCARE INFORMATICS, *AVOIDABLE COSTS IN U.S. HEALTHCARE: THE \$200 BILLION OPPORTUNITY FROM USING MEDICINES MORE RESPONSIBLY* 3 (2013), http://offers.premierinc.com/rs/381-NBB-525/images/Avoidable_Costs_in%20US_Healthcare-IHII_AvoidableCosts_2013%5B1%5D.pdf.

284. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173 (2003).

285. Theodore T. Lee et al., *The Politics of Medicare and Drug-Price Negotiation (Updated)*, HEALTH AFF. BLOG (Sept. 19, 2016), <https://www.healthaffairs.org/doi/10.1377/hblog20160919.056632/full>.

286. Mike McCaughan, *Medicare Part D: Medicare Part D Covers Retail Prescription Drugs for Medicare Beneficiaries Through Unique, Stand-Alone Drug Insurance Plans*, HEALTH AFF. HEALTH POL'Y BRIEF 1, 3 (2017).

287. Lydia Ramsey, *Members of Congress Just Took a Big Step Toward Tackling the Rising Cost of Prescription Drugs*, BUS. INSIDER (Feb. 28, 2017), <https://www.businessinsider.com/members-of-house-and-senate-introduce-drug-importation-bill-2017-2>.

288. Kevin Outterson & Aaron S. Kesselheim, *How Medicare Could Get Better Prices on Prescription Drugs*, HEALTH AFF. 832, 838 (2009) (describing how “[o]ver time, companies react to parallel trade to limit its scope and profitability”); Rafi Mohammed, *Cheap Drugs from Canada Won't Reduce Drug Prices*, HARV. BUS. REV. (Feb. 12, 2016), <https://hbr.org/2016/02/why-importing-cheap-pharmaceuticals-from-canada-wont-work>.

may experience higher out-of-pocket costs and premium costs.²⁸⁹ Most recently, the Department of Health and Human Services proposed ending the rebates that drug manufacturers pay to Medicare, asserting that drug prices will fall as a result.²⁹⁰ Others express concern that premiums will rise for Medicare beneficiaries as a result.²⁹¹ For its part, the 116th Congress has already made pharmaceutical drug pricing a central issue, highlighted by several new bills and hearings in both the House²⁹² and Senate²⁹³ in its first months.

In addition, many state legislatures have proposed initiatives to control drug costs. In 2016, Californians voted on a ballot measure to reduce public insurance program prices to the VA's lowest price. The pharmaceutical industry vigorously opposed the policy and voters ended up rejecting it.²⁹⁴ As of April 2019, forty-six states had introduced state-level drug pricing reform measures, including Maryland (a price gouging law that was overturned in court)²⁹⁵ and New York (a new approach to negotiating drug prices for its state Medicaid program);²⁹⁶ Vermont signed a bill into law in June 2016 mandating greater transparency for drug manufacturers' research and development costs.²⁹⁷

Others have suggested that drug pricing would be better addressed by strengthening the free market for medications, such that effective and better-

289. Thomas J. Hwang et al., *Analysis of Proposed Medicare Part B to part D Shift with Associated Changes in Total Spending and Patient Cost-Sharing for Prescription Drugs*, J. AM. MED. ASS'N 1, 1-2 (2019).

290. DEP'T OF HEALTH & HUM. SERV., FRAUD AND ABUSE: REMOVAL OF SAFE HARBOR PROTECTION FOR REBATES INVOLVING PRESCRIPTION PHARMACEUTICALS AND CREATION OF NEW SAFE HARBOR PROTECTION FOR CERTAIN POINT-OF-SALE REDUCTIONS IN PRICE ON PRESCRIPTION PHARMACEUTICALS AND CERTAIN PHARMACY BENEFIT MANAGER SERVICE FEES 2341 (2019), https://www.hhs.gov/sites/default/files/20190131_42-CFR-Part-1001.pdf.

291. Ike Swetlitz & Nicholas Florko, *In Bold New Proposal, Trump Administration Pitches an End to Certain Drug Rebates*, STAT NEWS (Jan. 31, 2019), <https://www.statnews.com/2019/01/31/in-bold-new-proposal-trump-administration-pitches-an-end-to-certain-drug-rebates>.

292. *Examining the Actions of Drug Companies in Raising Prescription Drug Prices: Hearing Before the H. Comm. On Oversight and Reform*, 116th Cong. (2019).

293. *Drug Pricing in America: A Prescription for Change, Part 1: Hearing Before the S. Comm. On Finance*, 116th Cong. (2019).

294. Deena Beasley, *California Voters Turn Down Drug Pricing Initiative*, Reuters (Nov. 9, 2016), <https://www.reuters.com/article/us-usa-election-pharmaceuticals/california-voters-turn-down-drug-pricing-initiative-idUSKBN134120>.

295. NAT'L ACAD. STATE HEALTH POL'Y, STATE LEGISLATIVE ACTION TO LOWER PHARMACEUTICAL COSTS (2019), <https://nashp.org/wp-content/uploads/2019/01/RxTracker-final-4.23.2019.pdf>; Pamela Wood, *Federal Appeals Court Deals Another Setback to Maryland Drug Price-Gouging Law*, BALT. SUN (July 25, 2018), <https://www.baltimore.sun.com/news/maryland/politics/bs-md-drug-price-ruling-20180725-story.html>.

296. Thomas J. Hwang et al., *Value-Based Pricing and State Reform of Prescription Drug Costs*, 318 J. AM. MED. ASS'N 609, 609 (2017).

297. Ed Silverman, *Vermont Becomes First State to Require Drug Makers to Justify Price Hikes*, STAT NEWS (June 6, 2016), <https://www.statnews.com/pharmalot/2016/06/06/vermont-drug-prices-transparency>.

priced products would be used more often while products that worked poorly, were unsafe, or were overpriced would fall out of use.²⁹⁸ In the U.K., the National Institute for Clinical Excellence has an important role in comparative cost-effectiveness and formulary determinations, given its power to exclude coverage for expensive drugs by the single government payor.²⁹⁹ Such an agency does not exist in the United States, and FDA approval of drugs is not predicated on a demonstration of comparative effectiveness or cost-effectiveness.³⁰⁰ In fact, such assessment is beyond the agency's enabling legislation. Agencies that have attempted to fill this function have faced strong political pressure. These include the now-disbanded Office of Technology Assessment³⁰¹ and the Agency for Healthcare Research and Quality.³⁰² As described on its website, the Agency for Healthcare Research and Quality conducts and supports health services research within research institutions, hospitals, and health care systems to better inform decision-making and to improve healthcare services, organization, and financing.³⁰³ Political concerns have led the agency to exert caution in supporting a broad range of cost-effectiveness studies.³⁰⁴

With the passage of the Affordable Care Act, it was expected that a new organization—eventually named the Patient Centered Outcomes Research Institute—would be created to serve the role of a comparative effectiveness research institute, to guide decisions on cost-effective clinical decision-making. Political forces also altered that group's mission, reducing its potential for supporting head-to-head comparisons of competing treatments.³⁰⁵ Then, before

298. Outterson & Kesselheim, *supra* note 288, at 838.

299. See e.g., NICE TECHNOLOGY APPRAISAL GUIDANCE, NAT'L INST. HEALTH CARE EXCELLENCE <https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance> (last visited May 18, 2019) (offering comprehensive templates and guidance for the technology appraisal process).

300. Applications for FDA Approval to Market a New Drug, 21 C.F.R. § 314.126 (2018).

301. OFFICE OF TECH. ASSESSMENT ARCHIVE, FEDERATION OF AMERICAN SCIENTISTS (2016), <https://ota.fas.org>; Ed O'Keefe, *When Congress Wiped an Agency Off the Map*, WASH. POST, (Nov. 29, 2011), https://www.washingtonpost.com/blogs/federal-eye/post/when-congress-wiped-an-agency-off-the-map/2011/11/29/gIQAIt0J9N_blog.html?utm_term=.202d3102d9bf.

302. See AGENCY FOR HEALTHCARE RESEARCH AND QUALITY, <https://www.ahrq.gov/> (last visited Apr. 16, 2019); see also Casey Ross, *This Federal Agency That Aims to Make Health Care More Effective Is on the Chopping Block, Again*, STAT NEWS (Mar. 30, 2017), <https://www.statnews.com/2017/03/30/ahrq-budget-trump-nih>.

303. AGENCY FOR HEALTHCARE RESEARCH AND QUALITY: A PROFILE (last visited Apr. 16, 2019), <https://www.ahrq.gov/cpi/about/profile/index.html>.

304. Peter J. Neumann et al., *Medicare and Cost-Effectiveness Analysis*, 353 NEW ENG. J. MED. 1516, 1516 (2005).

305. Nicholas Bagley, *Who Says PCORI Can't Do Cost Effectiveness?*, INCIDENTAL ECONOMIST (Oct. 14, 2013), <https://theincidentaleconomist.com/wordpress/who-says-pcori-cant-do-cost-effectiveness>.

it began its work, the Patient-Centered Outcomes Research Institute was forbidden from using quality-of-life data to determine cost-effectiveness in the standard manner.³⁰⁶ A number of private and non-profit organizations have moved into this space as well, including the Institute for Clinical and Economic Review, Alosa Health, and Consumer Report Best Buy Drugs,³⁰⁷ which have made value-based pricing of drugs more easily accessible, offering tools that allow providers to make better-informed prescribing decisions.³⁰⁸ The goal of these organizations is to foster cost-effective prescribing practices through outcomes-based assessments.³⁰⁹ As independent research organizations, such recommendations are often influential to policymakers but are non-binding to manufacturers setting list prices for pharmaceuticals. Pharmaceutical manufacturers are also experimenting with reimbursing for patients who do not respond to certain drug therapies—usually those that are new and expensive.³¹⁰

D. *Promotion to Clinicians and Patients*

Pharmaceutical manufacturers spend about \$30 billion dollars per year to promote their drugs to physicians and patients—this includes \$9.6 billion spent on direct-to-consumer advertising in 2016.³¹¹ Physician-targeted promotion occurs directly through sales representatives, as well as through sponsored Continuing Medical Education programs, distribution of free samples, recruitment of key opinion leaders to serve on speaker's bureaus and in other consulting capacities, and through nominally unrestricted educational grants. Considerable evidence documents the substantial impact of industry promotion on physician decision-making, including the association between pharmaceutical promotion and non-evidence-based prescribing. One study found that a single inexpensive meal from a pharmaceutical company was associated with increased prescribing practices.³¹² Advertising in print medical journals is another lucrative way of reaching and influencing physician prescribing practices; return-on-investment is between \$3-5 per dollar spent, and in 2016, \$637 million was spend on nearly 100,000 pages of medical

306. Limitations on Certain Uses of Comparative Clinical Effectiveness Research, 42 U.S.C. § 1320e-1 (2010).

307. Kesselheim et al., *supra* note 181, at 866.

308. Peter B. Bach & Steven D. Pearson, *Payer and Policy Maker Steps to Support Value-Based Pricing for Drugs*, 314 J. AM. MED. ASS'N 2503, 2503 (2015).

309. *Id.*

310. Dhruv S. Kazi et al., *Effect of Money-Back Guarantees on the Cost-Effectiveness of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors*, 168 ANNALS INTERNAL MED. 896, 897 (2018).

311. Lisa M. Schwartz & Steven Woloshin, *Medical Marketing in the United States, 1997-2016*, 321 J. AM. MED. ASS'N 80, 80 (2019).

312. Collette DeJong et al., *Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries*, 176 J. AM. MED. ASS'N 1114, 1114 (2016).

advertisements.³¹³ Many academic medical centers have placed restrictions on access to marketing representatives to counteract industry influence on prescribing behavior.³¹⁴ An alternative means by which physicians can receive unbiased information on prescribing practices is academic detailing,³¹⁵ in which several non-profit entities disseminate non-commercial reports to provide more balanced information.³¹⁶ Health systems often employ academic detailing to proactively market evidence-based prescribing recommendations.

Congress enacted the Physician Payments Sunshine Act as part of the Affordable Care Act in 2010 to require pharmaceutical and device manufacturers to report payments to physicians in a publicly accessible database.³¹⁷ The law sought to facilitate greater transparency about physician-industry relationships based on concern that physicians were being paid by industry sources for educational and other activities, which had the effect of distorting their prescribing choices.³¹⁸ Several studies have identified a correlation between physician payments from industry and Medicare Part D prescribing—as payments increased, so did brand-name prescribing behavior.³¹⁹

The United States and New Zealand are the only two countries that permit drug manufacturers to engage in broad direct-to-consumer marketing of prescription drugs.³²⁰ Direct-to-consumer advertising increased markedly in the United States after 1997, when the FDA promulgated a new rule enabling

313. Michael S. Sinha et al., *Pharmaceutical Advertising in Medical Journals: Revisiting a Long-Standing Relationship*, 153 CHEST J. 9, 9 (2018).

314. Troyen A. Brennan et al., *Health Industry Practices that Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 J. AM. MED. ASS'N 429, 429-30 (2006).

315. Jerry Avorn, *Academic Detailing: "Marketing" the Best Evidence to Clinicians*, 317 J. AM. MED. ASS'N 361, 361 (2017).

316. Michael A. Fischer & Jerry Avorn, *Academic Detailing Can Play a Key Role in Assessing and Implementing Comparative Effectiveness Research Findings*, 31 HEALTH AFF. 2206, 2207 (2012).

317. Transparency Reports and Reporting of Physician Ownership or Investment Interests, 42 C.F.R. Parts 402 and 403 (2016); Neil M. Kirschner et al., *Health Policy Basics: The Physician Payment Sunshine Act and the Open Payments Program*, 161 ANNALS INTERNAL MED. 519, 519 (2014); see e.g., FEBRUARY 2019 MEDICAID & CHIP ENROLLMENT DATA HIGHLIGHTS, <https://www.medicaid.gov/medicaid/program-information/medicaid-and-chip-enrollment-data/report-highlights/index.html> (last visited May 19, 2019).

318. Michael S. Sinha & Aaron S. Kesselheim, *The Effects of the Sunshine Act: What Can and Should We Expect?*, 17 AM. J. BIOETHICS 22, 22 (2017).

319. Roy H. Perlis & Clifford S. Perlis, *Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs*, 11 PUB. LIBR. SCI. ONE 1, 5-6 (2016); Aaron Kessler et al., *The More Opioids Doctors Prescribe, the More Money They Make*, CNN EXCLUSIVE (2018), <https://www.cnn.com/2018/03/11/health/prescription-opioid-payments-eprise/index.html>.

320. Jeremy A. Greene & Elizabeth S. Watkins, *The Vernacular of Risk -- Rethinking Direct-to-Consumer Advertising of Pharmaceuticals*, 373 NEW ENG. J. MED. 1087, 1087 (2015).

routine direct-to-consumer advertising over television.³²¹ In the last twenty years, direct-to-consumer advertising has increased by approximately 450%, and now represents nearly one-third of all pharmaceutical advertising in the United States.³²² Studies have documented the effect of such advertising on increasing patient demand for advertised products—usually high-cost brand-name drugs—thereby likely increasing health care expenditures.³²³ Some point out the role of such advertising in informing patients of the availability of treatments for conditions patients may not have known were treatable (e.g., incontinence, restless leg syndrome),³²⁴ which encourages greater patient autonomy.³²⁵ One criticism of direct-to-consumer advertising is that such advertisements overstate the benefits of drugs while underestimating risks, for example, by describing those risks in the context of positive imagery in the background of the ad.³²⁶ A newer theme in direct-to-consumer advertising has been unbranded ads, which often direct patients to a website purporting to provide disease-specific education; a few clicks later leads to a brand-name drug advertisement.³²⁷ In one extreme case, researchers identified a rare disease drug advertisement on the television soap opera *General Hospital*; the pharmaceutical manufacturer, Incyte, worked with the producers of the show to raise awareness about the polycythemia vera, but their product may have been subtly promoted as a viable alternative to symptomatic treatment.³²⁸

Though physicians can prescribe FDA-approved medications for any non-FDA-approved use they deem appropriate, the FDA has long restricted manufacturers' ability to promote such off-label uses, subject to certain safe harbors.³²⁹ Though generally prohibited, off-label promotional activity has historically been permitted in the limited contexts of unsolicited questions from providers, distribution of reprints of peer-reviewed articles, and impartial

321. FDA, GUIDANCE FOR INDUSTRY: CONSUMER-DIRECTED BROADCAST ADVERTISEMENTS (1999); Lisa M. Schwartz & Steve Woloshin, *Medical Marketing in the United States, 1997-2016*, 32 J. AM. MED. ASS'N 80, 82-86 (2019).

322. Schwartz, *supra* note 321, at 80.

323. Min H. Wu et al., *Trends in Direct-to-Consumer Advertising of Prescription Contraceptives*, 93 CONTRACEPTION 398, 402-04 (2016).

324. Sidney M. Wolfe, *Direct-to-Consumer Advertising: Education or Emotion Promotion?*, 346 NEW ENG. J. MED. 524, 526 (2002).

325. Crystal Adams, *Direct-to-Consumer Advertising of Prescription Drugs Can Inform the Public and Improve Health*, 2 J. AM. MED. ASS'N ONCOLOGY 1395, 1395 (2016).

326. Natasha Parekh & William H. Shrank, *Dangers and Opportunities of Direct-to-Consumer Advertising*, 33 J. GEN. INTERNAL MED. 586, 586-87 (2018).

327. Rebecca Robbins, *Behind the Stealth Ad Campaigns for the EpiPen and Other Drugs*, STAT NEWS (Aug. 29, 2016), <https://www.statnews.com/2016/08/29/epipen-unbranded-ads>.

328. Sham Mailankody & Vinay Prasad, *Pharmaceutical Marketing for Rare Diseases: Regulating Drug Company Promotion in an Era of Unprecedented Advertisement*, 317 J. AM. MED. ASS'N 2479, 2479 (2017).

329. Jerry Avorn et al., *Forbidden and Permitted Statements about Medications: Loosening the Rules*, 373 NEW ENG. J. MED. 967, 967 (2015).

continuing medical education that is impartial.³³⁰ Nonetheless, the practice has been common outside of these safe harbors, and has been an important driver of drug expenditures as well as of adverse clinical outcomes.³³¹ Illegal off-label marketing has led to litigation against nearly every major drug company in the past decade and resulted in over \$35 billion dollars in civil and criminal fines from 1991 to 2015.³³² Many drug companies have been compelled to enter into corporate integrity agreements with the Office of the Inspector General, intended to prevent further illegal behavior by providing government oversight of their marketing compliance.³³³ However, the penalties for such behavior, even when large, are generally far less than the increased revenue that such practices generate.³³⁴ One reason for this is that most cases are actually settled and the fines are negotiated between the government and the manufacturer, and not imposed by a court.³³⁵

Restrictions on off-label marketing have come under attack by evolving judicial interpretations of the First Amendment and its protection of commercial speech.³³⁶ Courts have been receptive to the notion that off-label promotion is a speaker-based restriction that does not meet a heightened level of justification because less restrictive alternatives are possible, such as adding disclaimers.³³⁷ However, there is evidence that such disclaimers do not change product-related knowledge or prescribing behavior.³³⁸ The pharmaceutical industry contends that that companies should be allowed to disseminate any information about their products as long as it is not false or misleading.³³⁹ Interestingly, the FDA generally does not review content of advertisements before publication and has claimed that federal law prevents the agency from

330. Michael S. Sinha & Aaron S. Kesselheim, *The Next Forum for Unraveling FDA Off-Labeling Marketing Rules: State and Federal Legislatures*, 15 PUB. LIBR. SCI. MED. 1, 1 (2018).

331. *Id.*

332. SAMMY ALMASHAT ET AL., TWENTY-FIVE YEARS OF PHARMACEUTICAL INDUSTRY CRIMINAL AND CIVIL PENALTIES: 1991 THROUGH 2015, at 5-17 (Public Citizen, 2016).

333. Michelle M. Mello, et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 15, 1557, 1558 (2009).

334. Aaron S. Kesselheim et al., *False Claims Act Prosecution Did Not Deter Off-Label Drug Use in the Case of Neurontin*, 30 HEALTH AFF. 2318, 2324-25 (2011).

335. U.S. GOV'T ACCOUNTABILITY OFFICE, FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES 19, 22, 28 (2008), <https://www.gao.gov/new.items/d08835.pdf>.

336. Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J. L. & MED. 225, 242-47 (2011).

337. Thompson v. W. States Med. Ctr., 535 U.S. 357, 376 (2002).

338. Aaron S. Kesselheim et al., *Mandatory Disclaimers on Dietary Supplements Do Not Reliably Communicate the Intended Issues*, 34 HEALTH AFF. 438-46 (2015).

339. *Thompson*, 535 U.S. at 367; *United States v. Caronia*, 703 F.3d 149, 160 (2d Cir. 2012).

requiring such pre-review prior to use.³⁴⁰ Recently, several states have passed laws loosening off-label promotion standards, though these are likely to be superseded by federal law.³⁴¹ The 21st Century Cures Act allows manufacturers to directly discuss “health care economic information” with payors related to off-label uses, and two bills have been proposed in Congress as well.³⁴² The FDA continues to debate the topic and appears ready to loosen restrictions on such advertising, even if data supporting off-label use are based on less rigorous studies that would likely be insufficient to obtain a supplemental indication for that population.³⁴³

IV. INTRODUCTION OF GENERIC DRUGS

When a brand-name drug’s market exclusivity period ends, generic drugs—versions of the brand-name drug often produced by different manufacturers—can enter the market. The Hatch-Waxman Act created an abbreviated process for the approval of generic drugs, such that to secure approval, a manufacturer must only prove bioequivalence to the corresponding innovator drug.³⁴⁴ Meeting this standard requires the performance of comparatively small pharmacokinetic and pharmacodynamic studies to show comparable bioavailability to the brand-name version.³⁴⁵ If these studies demonstrate delivery of the same active ingredient into the body in the same concentration and with the same timing, clinical trials in large numbers of patients are not necessary.³⁴⁶ Generic drugs must also be pharmaceutically equivalent, meaning that they cannot be a different formulation. Decades of safe and effective generic drug use has validated the rigorousness of the FDA’s bioequivalence standards and the association between bioequivalence and clinical equivalence of brand-name and generic drugs. However, a minority of

340. FDA, *PRESCRIPTION DRUG ADVERTISING: QUESTIONS AND ANSWERS* (2015), https://www.fda.gov/drugs/prescription-drug-advertising/prescription-drug-advertising-questions-and-answers#approve_advertisements.

341. Michael S. Sinha & Aaron S. Kesselheim, *The Next Forum for Unraveling FDA Off-Label Marketing Rules: State and Federal Legislatures*, 15 *PUB. LIBR. SCI. MED.* 1, 1-3 (2018).

342. *Id.*

343. FDA, *PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS* 33-44 (2017).

344. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

345. Abbreviated New Drug Applications, 21 U.S.C. § 355(j) (2018).

346. *Id.*

physicians still harbors skepticism about the safety and efficacy of generic drugs.³⁴⁷

Drug product selection laws in each state allow or mandate pharmacists to substitute generic drugs for brand-name drugs, even if a physician wrote the prescription for a brand-name product. However, the scope of these laws varies considerably. One study notes that twenty states allow automatic substitution but another twenty-five states only allow substitution with patient approval.³⁴⁸ In a small minority of cases, physicians will continue to prescribe branded drugs even when generic drugs are available; automatic generic substitution is undermined in 3-5% of prescriptions when physicians write “dispense as written.”³⁴⁹

Though a generic drug’s label must match that of its equivalent brand-name counterpart, brand-name manufacturers may exit the market after generic approval—or divert their active post-market surveillance resources away from those products. Arguably, the Supreme Court’s ruling in *Mutual Pharmaceutical v. Bartlett* eliminated incentives for generic manufacturers to conduct post-approval surveillance in a multi-source environment by declining to hold generic manufacturers liable for labeling changes.³⁵⁰ Therefore, much of the responsibility for funding, conducting, and reporting on research on the adverse effects of generic drugs has fallen to academic and government researchers. The FDA has proposed regulations that would obligate generic drug manufacturers to monitor the safety of their products and to make appropriate label changes, regardless of whether the warning is present on the innovator manufacturer drug label.³⁵¹ The FDA withdrew the rule in December 2018 upon receipt of complaints from the generic manufacturing lobby that it would be unduly burdensome and increase generic pharmaceutical costs.³⁵²

Notably, generic drugs are not required to resemble the brand-name version (or other generic versions). The FDA considers pill appearance (color, shape, size, texture) to be an aesthetic property, and brand-name manufacturers

347. Aaron S. Kesselheim et al., *Prevalence and Predictors of Generic Drug Skepticism Among Physicians: Results of a National Survey*, 176 J. AM. MED. ASS’N INTERNAL MED. 845, 845-47 (2016).

348. Ameet Sarpatwari & Aaron S. Kesselheim, *The Case for Reforming Drug Naming: Should Brand Name Trademark Protections Expire upon Generic Entry?*, 13 PUB. LIBR. SCI. MED. 1, 1-6 (2016).

349. William H. Shrank et al., *The Consequences of Requesting Dispense as Written*, 124 AM. J. MED. 309, 314-17 (2011).

350. 570 U.S. 472, 473 (2013).

351. Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67985 (proposed Nov. 13, 2013).

352. Thomas M. Burton, *FDA Withdraws Proposed Rule That Would Have Exposed Generic-Drug Makers to Liability*, WALL ST. J. (Dec. 31, 2018), <https://www.wsj.com/articles/fda-withdraws-proposed-rule-that-would-have-exposed-generic-drug-makers-to-liability-11544726478>.

will sometimes claim trade dress rights in the appearance of their drugs³⁵³ particularly in cases in which the drugs' appearance is distinctive, such as the "purple pill" of omeprazole (Prilosec) and the "pale blue diamond" shape of sildenafil (Viagra). Because FDA does not require consistency in generic pill appearance, patients often experience changes in their pill appearance during routine refills or during switches from brand-name to generic drugs. Several studies have demonstrated that variations in appearance contribute to non-adherence.³⁵⁴ In a recent survey of patients, the majority of respondents identified the correct medication based on pill appearance; their preferences were for consistent color, shape, and size of pills when medications are refilled.³⁵⁵

To reach the market, generic drug manufacturers generally must wait until patents covering the brand-name drug have expired.³⁵⁶ Generic manufacturers may also attempt to enter the market early by issuing a special challenge, a Paragraph IV certification. This requires that the generic manufacturer certify that it can demonstrate noninfringement (that their bioequivalent product is not covered by unexpired patents) or invalidity (that the listed patents are invalid for any reason).³⁵⁷ For small-molecule drugs, all patents covering the product are listed by the brand-name company in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, colloquially known as the Orange Book.³⁵⁸ The brand manufacturer receives notification of Paragraph IV challenges and will often pursue patent infringement litigation in response; this automatically delays FDA generic drug approval by thirty months to provide time to litigate the matter.³⁵⁹ Such litigation is generally more successful against the brand-name drug patent when brought against secondary patents, as opposed to the original small molecule patent that formed the basis for FDA approval.

353. Jeremy A. Greene & Aaron S. Kesselheim, *Why Do the Same Drugs Look Different? Pills, Trade Dress, and Public Health*, 365 *NEW ENG. J. MED.* 83, 83-89 (2011).

354. Aaron S. Kesselheim et al., *Variations in Pill Appearance of Antiepileptic Drugs and the Risk of Nonadherence*, 173 *J. AM. MED. ASS'N INTERNAL MED.* 202-08 (2013); Aaron S. Kesselheim et al., *Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction: Cohort and Nested Case-Control Studies*, 161 *ANNALS INTERNAL MED.* 96-103 (2014).

355. Ameet Sarpatwari et al., *A Survey of Patients' Perceptions of Pill Appearance and Responses to Changes in Appearance for Four Chronic Disease Medications*, 34 *J. GEN. INTERNAL MED.* 420, 420-28 (2019).

356. Patent Certification, 21 C.F.R. § 314.94(a)(12)(i)(A)(2) (2015).

357. See Paragraph IV Challenge, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2018).

358. See Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs Could be Extended for Decades*, 31 *HEALTH AFF.* 2286, 2291 (2012).

359. Aaron S. Kesselheim et al., *"Pay for Delay" Settlements of Disputes Over Pharmaceutical Patents*, 365 *NEW ENG. J. MED.* 1439, 1440 (2011).

Given the often-substantial legal fees associated with such a challenge, the Hatch-Waxman Act established a 180-day period of generic market exclusivity for any generic manufacturers that are first to file a successful Paragraph IV certifications.³⁶⁰ Prices may not fall significantly during this 180-day market duopoly period, and brand-name manufacturers often introduce their own authorized generics to protect its market share. Authorized generics are versions of the brand-name medicine sold as a generic and based on original FDA approval data (no bioequivalence testing is necessary).³⁶¹ They are intended to extract market share from the generic manufacturer during the 180-day duopoly period and beyond.

A. *Strategies to Delay Entry of Generic Drugs*

While the network of federal and state laws is designed to facilitate introduction of generic drugs—and subsequently, rapid declines in price—it frequently does not work out that way in reality. Over the past two decades, brand-name manufacturers have designed various strategies that work to delay timely introduction of generic drugs. Some of these strategies leverage the very regulatory requirements that were intended to facilitate generic drug introduction, and other strategies are conducted in collaboration with generic manufacturers.³⁶² All are prime examples of the dysfunction of the U.S. pharmaceutical market.

Numerous formal programs and business tactics can delay the entry of generic drugs. For instance, in 1997, new legislation offered manufacturers six additional months of market exclusivity if they studied the effects of their drugs in children, regardless of study outcome. Study type and size was negotiated upon FDA issuance of a written request, but the company could also petition FDA to issue a written request. One study focusing on a subset of pediatric trials performed between 2002-2004 found that for every dollar a company spent on pediatric trials, it generated over \$14 in revenues as a result of the six month market exclusivity.³⁶³ A more recent study looking at pediatric

360. 21 U.S.C. § 355(j)(5)(B)(iv) (2018). Generally, Paragraph IV certification are awarded to a single manufacturer, but on occasion, two or more manufacturers will be required to share 180-day exclusivity. Ernst R. Berndt et al., *Authorized Generic Drugs, Price Competition, And Consumers' Welfare*, 26 HEALTH AFF. 790, 793-94 (2007).

361. Jing Luo et al., *Effect of Generic Competition on Atorvastatin Prescribing and Patients' Out-of-Pocket Spending*, 176 J. AM. MED. ASS'N INTERNAL MED. 1317, 1317 (2016); see also Zachary Brennan, *Authorized Generics: Why Mylan Would Compete With Itself in the EpiPen Market*, REGULATORY FOCUS (Aug. 29, 2016), <https://www.raps.org/regulatory-focus/E2%84%A2/news-articles/2016/8/authorized-generics-why-mylan-would-compete-with-itself-in-the-epipen-market>.

362. Aaron S. Kesselheim et al., *Determinants of Market Exclusivity for Prescription Drugs in the United States*, 177 J. AM. MED. ASS'N INTERNAL MED. 1658, 1658 (2017).

363. Jennifer S. Li et al., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 J. AM. MED. ASS'N 480, 483 (2007).

exclusivity awards from 2007-12 found high costs to consumers, particularly for blockbuster drugs.³⁶⁴ As of December 2018, 242 approved drugs have been granted pediatric exclusivity.³⁶⁵

Settlements of litigation arising from Paragraph IV challenges are another key contributor to delaying generic entry. The most controversial type of settlement involves a *quid pro quo*: the challenge will be dropped, but the generic challenger will receive something of value in return. The Federal Trade Commission (FTC) has opposed “pay for delay” settlements, and the Supreme Court affirmed the FTC’s authority to review such cases in *FTC v. Actavis* (2013).³⁶⁶ The disputed agreement in that case was between Actavis and Solvay Pharmaceuticals; Actavis agreed not to bring its generic formulation of Solvay’s testosterone formulation (Androgel) to the market for several years—even though it had already received ANDA approval—in exchange for shared marketing responsibilities and profits from Androgel. Settlements with payments have decreased in number since the *Actavis* decision, but agreements involving transfers of value other than cash (e.g., a license to market an authorized generic) have continued. Settlements for biosimilars seeking to compete with adalimumab [Humira], for instance, involve agreed-upon delays in market entry, while paying royalties for licensing remaining patents until expiration of all remaining patents.³⁶⁷ It is unclear under what conditions these newer forms of settlements can similarly run afoul of antitrust law.³⁶⁸

Among the business tactics used to delay generic entry include securing so-called “secondary” patents that cover aspects of a drug like its coating or method of administration.³⁶⁹ For example, a study of the HIV drugs ritonavir and lopinavir found over 100 secondary patents on the two drugs covering related chemical structures, compositions or formulations, manufacturing methods and processes, and methods of disease treatment, adding twelve additional years to the drugs’ market exclusivity periods.³⁷⁰ Patents are

364. See Michael S. Sinha et al., *Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension, 2007 to 2012*, 178 J. AM. MED. ASS’N INTERNAL MED. 1458, 1458-59 (2018).

365. PEDIATRIC EXCLUSIVITY GRANTED, FDA <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm> (last visited Apr. 9, 2019).

366. Fed. Trade Comm’n v. Actavis, 133 S. Ct. 2223, 2227 (2013).

367. *Pfizer Becomes Latest to Settle with AbbVie Over Humira*, CTR. FOR BIOSIMILARS (Dec. 3, 2018), <https://www.centerforbiosimilars.com/news/pfizer-becomes-latest-to-settle-with-abbvie-over-humira>.

368. Michael Carrier, *FTC v. Actavis: Where We Stand After 5 Years*, IP WATCHDOG (June 18, 2018), <https://www.ipwatchdog.com/2018/06/18/ftc-v-actavis-stand-5-years/id=98536>.

369. Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of “Secondary” Pharmaceutical Patents*, PUB. LIBR. SCI. ONE 1, 1, 2 (Oct. 2012).

370. Tahir Amin & Aaron S. Kesselheim, *supra* note 358, at 2289 tbl.1.

intended to apply only to those inventions that are truly novel³⁷¹ and non-obvious³⁷² to skilled practitioners based on what is already known in the field. Yet lax enforcement of pharmaceutical patenting standards has made it relatively easy to patent aspects of a drug such as coating or alternate chemical versions, polymorphs, or other salts or crystalline structures. In the case of omeprazole (Prilosec), the United States Patent and Trade Office granted AstraZeneca a patent on the derivative product—esomeprazole (Nexium)—that was simply its left-handed isomer, with little or no clinical difference.³⁷³ Esomeprazole could have failed the novelty requirement because it was already included as a component of the racemic omeprazole patent. In fact, a Canadian court held that the esomeprazole patent was non-obvious, although they ultimately invalidated it on different grounds.³⁷⁴

Obtaining secondary patents can help facilitate “product hopping,” which occurs when a manufacturer of a brand-name drug introduces a slightly modified new product, such as a new film as opposed to the original tablet, or an extended-release version of an immediate-release product.³⁷⁵ In those cases, innovator manufacturers have attempted to cease or limit distribution of the original product prior to the expiry of its market exclusivity, effectively forcing patients onto the new product. Then, if a generic comes out to the original version, substitution with the new formulation is not possible.³⁷⁶ For example, Abbott twice introduced new formulations of fenofibrate (TriCor)—first by moving from capsules to tablets, then by slightly altering the tablet strength as the generic version was ready to launch.³⁷⁷ In such circumstances, generic manufacturers can either try to launch with the original version, but will find fewer prescribers of that older version (generic manufacturers do not promote their products, making it harder to convince prescribers to use the older version). Alternatively, the generic can seek to reformulate its product, although it would take additional time for the new formulation to earn FDA

371. 35 U.S.C. § 102 (2015).

372. 35 U.S.C. § 103 (2011).

373. Walid F. Gellad et al., *Assessing the Chiral Switch: Approval and Use of Single-Enantiomer Drugs, 2001 to 2011*, 20 AM. J. MANAGED CARE 90, 90 (2014).

374. Sanjaya Mendis & David Tait, *Canada Patent Litigation: Federal Court Rules “Enhanced Disclosure” Requirement for Sound Prediction Applies Only To “New Use” Patents*, MCCARTHEY TETRAULT (July 11, 2014), <https://www.mccarthy.ca/en/insights/blogs/snippets/canada-patent-litigation-federal-court-rules-enhanced-disclosure-requirement-sound-prediction-applies-only-new-use-patents>.

375. Reed F. Beall et al., *New Drug Formulations and Their Respective Generic Entry Dates*, 25 J. MANAGED CARE & SPECIALTY PHARMACY 218, 218 (2019).

376. John S. Sears, *The Evolving Standard of Antitrust Analysis in Pharmaceutical Product Hopping*, J. BUS. & INTELL. PROP. L. (Aug. 31, 2015), <http://ipjournal.law.wfu.edu/2015/08/the-evolving-standard-of-antitrust-analysis-in-pharmaceutical-product-hopping>.

377. *Abbott Labs. v. Teva Pharm.*, 432 F. Supp. 2d 408, 415-18 (D. Del. 2006).

approval.³⁷⁸ In another case, Warner Chilcott successively introduced formulations of doxycycline hyclate (Doryx), ranging from capsules to tablets to new strengths to tablet scoring changes.³⁷⁹ In certain circumstances, drug manufacturers have tried to discontinue production of the original version, which would make FDA approval of a generic more challenging. For example, Actavis sought to discontinue its immediate-release, twice-daily formulation of memantine (Namenda), a treatment for Alzheimer's disease-related dementia, prior to loss of market exclusivity, while introducing an extended-release, once-daily version. This product hop would have extended the market exclusivity of memantine by about fourteen years.³⁸⁰ However, in this case, the New York Attorney General successfully sued to enjoin the strategy and ensure that generics of the original immediate-release version could get on the market.

The America Invents Act of 2012 created a mechanism, known as *inter partes* review, allowing patent challenges for novelty or obviousness before a newly created entity, the Patent Trial and Appeal Board.³⁸¹ Any party, including a generic manufacturer, or even an interested individual, can challenge drug patents through the *inter partes* review process.³⁸² Brand-name/generic settlements of *inter partes* review challenges have also been increasing in frequency, though settlements do not ensure that *inter partes* review proceedings will not continue, particularly when such settlements occur late in the review process.³⁸³

Finally, brand-name manufacturers' generic-delaying tactics sometimes involve leveraging regulatory requirements. For example, some manufacturers have filed repetitive Citizen Petitions with FDA arguing that additional testing is needed before generic drugs can be approved; such petitions are usually rejected, but must be duly reviewed by FDA irrespective of merit.³⁸⁴ Manufacturers with drugs distributed under REMS

378. Samuel Howard, *Abbott Settles TriCor Class Action For \$184M*, LAW360 (Nov. 20, 2008), <http://www.law360.com/articles/77718/abbott-settles-tricor-class-action-for-184m>.

379. *Mylan Pharm. v. Warner Chilcott Pub.*, No. 12-3824, 2013 U.S. Dist. LEXIS 152467, at *14 (E.D. Pa. June 11, 2013).

380. *New York ex rel. v. Actavis*, 787 F.3d 638, 647 (2015); Vincent C. Capati & Aaron S. Kesselheim, *Drug Product Life-Cycle Management as Anticompetitive Behavior: The Case of Memantine*, 22 J. MANAGED CARE & SPECIALTY PHARMACY 339, 340 fig.1 (2016).

381. 35 U.S.C. § 314 (2012).

382. Carolyn L. Treasure & Aaron S. Kesselheim, *How Patent Troll Legislation Can Increase Timely Access to Generic Drugs*, 176 J. AM. MED. ASS'N INTERNAL MEDICINE 729, 729 (2016).

383. Jonathan J. Darrow et al., *Will Inter Partes Review Speed US Generic Drug Entry?*, 25 NATURE BIOTECHNOLOGY 1139, 1140 (2017); Jonathan J. Darrow et al., *The Generic Drug Industry Embraces a Faster, Cheaper Pathway for Challenging Patents*, 17 APPLIED HEALTH ECON. & HEALTH POL'Y 47, 47 (2019).

384. Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305, 308 (2016).

also can delay generic approval by refusing to share information about their REMS programs with generic manufacturers. One study found that such tactics produced \$5.4 billion in revenues to innovator manufacturers from delayed generic entry.³⁸⁵ Some brand-name manufacturers have attempted to prevent generic manufacturers from conducting bioequivalence testing by thwarting them from obtaining samples of the reference product, leading the FDA to publish a list naming the alleged offenders.³⁸⁶ The FTC has also stated that a refusal to provide generic manufacturers with innovator samples could constitute anticompetitive behavior under antitrust law.³⁸⁷ The U.S. House (FAST Generics Act) and Senate (CREATES Act) introduced legislation in the 115th Congress that would mandate sample sharing and help address this particular problem.³⁸⁸ Both have bipartisan support and should be enacted in the current Congress.

Some brand-name manufacturers have resorted to questionably anticompetitive practices in an attempt to preserve market share. Ongoing litigation accuses brand-name insulin manufacturers³⁸⁹ and generic drug manufacturers,³⁹⁰ respectively, of violating antitrust laws by coordinating price increases. More recently, brand-name manufacturers have engaged in practices of exclusive dealing and bundling in an attempt to exclude competition and preserve market share.³⁹¹ When considered jointly with pay-for-delay settlements, antitrust law may have a considerable impact on drug prices moving forward depending on the degree of federal enforcement.

385. ALEX BRILL, LOST PRESCRIPTION DRUG SAVINGS FROM USE OF REMS TO DELAY GENERIC MARKET ENTRY 1 (July 2014), https://static1.1.sqspcdn.com/static/f/460582/25228342/1406034596510/REMS_Study_July.pdf.

386. REFERENCE LISTED DRUG (RLD) ACCESS INQUIRIES, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm607738.htm> (last visited Apr. 9, 2019).

387. See BRILL, *supra* note 385, at 2.

388. THE CREATING AND RESTORING EQUAL ACCESS TO EQUIVALENT SAMPLES (CREATES) ACT OF 2019: ENDING THE ABUSIVE TACTICS THAT DELAY PATIENT ACCESS TO MORE AFFORDABLE MEDICINE 1 (2019), <https://www.leahy.senate.gov/imo/media/doc/020519%20116th%20CREATES%20Fact%20Sheet1.pdf>; Ameet Sarpatwari & Aaron S. Kesselheim, *Ensuring Timely Approval of Generic Drugs*, HEALTH AFF. BLOG (Mar. 25, 2015), <http://healthaffairs.org/blog/2015/03/24/ensuring-timely-approval-of-generic-drugs>.

389. Complaint at ¶ 294, *Chaires et al. v. Sanofi US, Novo Nordisk, Inc., and Eli Lilly and Co.*, 2017 WL 467734 (D.N.J.) (No. 3:17-cv-00699).

390. *In re Generic Pharmaceuticals Pricing Antitrust Litigation*, No. 16-CB-27240, 2019 WL 653854, at *5-6 (E.D. Pa. Feb. 15, 2019).

391. Michael S. Sinha et al., *Antitrust, Market Exclusivity, and Transparency in the Pharmaceutical Industry*, 319 J. AM. MED. ASS'N 2271, 2271 (2018).

B. Biosimilars

For many years, follow-on versions of biologic drugs, which are more complicated protein-based drugs, did not have a clear pathway to FDA approval. All biologic drugs had *de facto* permanent regulatory exclusivity free from direct competition. To solve this policy problem, the BPCIA created two possible categories of follow-on biologics: (1) biosimilars, follow-on biologics with no clinically meaningful structural differences from an innovator biologic; and (2) interchangeables, follow-on biologics with no differences that can also be safely substituted for an innovator biologic.³⁹² The FDA released draft guidance on how to obtain an interchangeable designation,³⁹³ but no product to date has received this designation.

The BPCIA also created a complicated procedure for determining whether market entry of a biosimilar would infringe upon innovator patents.³⁹⁴ Some lawyers have argued that as part of this process, follow-on biologic manufacturers must share their approval applications with innovator manufacturers.³⁹⁵ Because such disclosures could include trade secrets, there is concern over the potential utility of the follow-on biologic pathway. Recently, the Court of Appeals for the Federal Circuit ruled that application sharing was not a pre-requisite.³⁹⁶ Thirteen biosimilars have been approved though this route through October 2018, though far fewer are currently marketed due to ongoing litigation and settlements.³⁹⁷

More biosimilars have been introduced in settings around the world where regulatory approval pathways are in place, such as Europe (pathway created in 2005), Japan (2009) and South Korea (2010). National purchasing strategies in some of those countries can allow introduction of biosimilars to lower prices substantially, as compared to the patchwork of purchasers in the U.S. markets. By contrast, legal battles slowing entry of biosimilars into the U.S. market together will produce a U.S. biosimilar marketplace that will not reach the level of price competition seen in the generic small-molecule drug space.³⁹⁸

392. 42 U.S.C. § 262(k).

393. *Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry*, FOOD & DRUG ADMIN. (Jan. 2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>.

394. 42 U.S.C. § 262(l) (2016); Armeet Sarpatwari et al., *Progress and Hurdles for Follow-on Biologics*, 372 NEW ENG. J. MED. 2380, 2381 (2015).

395. Sarpatwari, *supra* note 394, at 2381.

396. *Amgen v. Apotex*, 794 F.3d 1347, 1357 (Fed. Cir. 2015), *rev'd in part, vacated in part*, 137 S. Ct. 1664 (2017).

397. Ameet Sarpatwari et al., *The U.S. Biosimilar Market: Stunted Growth and Possible Reforms*, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 92, 92 (2019).

398. *Id.*

C. Generic Drug Prices

The vast majority of generic drugs are extremely inexpensive for payors. However, the fundamental principle related to the generic drug market is that direct competition among multiple manufacturers is required to keep generic drugs inexpensive. As indicated above, if there was a Paragraph IV challenge, the 180-day period after the brand-name drug's market exclusivity ends may be characterized by a duopoly, in which prices do not fall substantially. In some cases, multiple generic manufacturers may share the 180-day generic exclusivity period due to simultaneous Paragraph IV challenges. More generic manufacturers might enter the market after that six-month period, leading prices to fall further. During this period, the brand-name manufacturer may continue to sell and market the brand-name drug, in an attempt to retain "price-inelastic" consumers who will buy the brand-name version no matter the price.³⁹⁹ In some cases, brand-name manufacturers contract directly with generic manufacturers to sell so-called "authorized generics," which are clinically indistinguishable from independent generic drugs.⁴⁰⁰

Since all FDA-approved generic drugs are, by definition, interchangeable with the brand-name version, the manufacturers in the market will compete on price. Generic drugs achieve low prices because they can be interchanged with each other and with brand-name versions at the pharmacy; thus, patients often do not know which manufacturer is supplying their generic drug. Also as a result, generic manufacturers have minimal incentive to spend money on marketing and instead concentrate on selling high-quality products, leading prices to be driven down to close to the cost of manufacturing by competition among generics. Generic drugs are least expensive when multiple firms drive down the price of generic drugs as each new generic entrant tries to gain market share by offering lower prices.⁴⁰¹ Generic drug prices drop as more competitors enter the market. A 2005 FDA study found that for a given brand-name drug, generic prices drop as more generic competitors enter the market, starting at 52% of the brand-name price with two generic competitors and reaching 13%

399. Ameet Sarpatwari & Aaron S. Kesselheim, *Navigating the Dermatological Drug Cost Curve*, 315 J. AM. MED. ASS'N 2724, 2725 (2016). So-called "narrow therapeutic index" drugs may be particularly appealing to price inelastic customer. These are drugs that have narrow windows between their therapeutic and toxic blood levels, so even small changes in concentration can make them ineffective (or dangerous). Examples include antiepileptic drugs, antiarrhythmic drugs and thyroid hormone replacement. Certain physicians prefer not to use generic version of narrow therapeutic index drugs, even though substitution of generic versions of these products appears to be safe for the vast majority of patients in most circumstances.

400. Rishi J. Desai et al., *Differences in Rates of Switchbacks After Switching from Branded to Authorized Generic and Branded to Generic Drug Products: Cohort study*, 361 BRIT. MED. J. 1180, 1180 (2018).

401. Chintan V. Dave et al., *Prices of Generic Drugs Associated with Numbers of Manufacturers*, 377 NEW ENG. J. MED. 2597, 2597 (2017).

or lower for fifteen or more competitors.⁴⁰² This trend was replicated using commercial claims data from 2008-2014.⁴⁰³ So-called “\$4 generic” programs and tiered formulary co-pays allow these savings to be passed on to consumers as well.⁴⁰⁴

However, supply and demand economics for generic drugs also mean that as generic manufacturers cease production of a particular generic drug, the price offered by the remaining manufacturers may rise.⁴⁰⁵ Thus, consolidation within the generic manufacturing industry may result in increased generic prices over time. There have also been instances where FDA inspections or drug recalls due to safety have narrowed the market for a particular generic drug, allowing for price hikes.⁴⁰⁶ In the case of digoxin, a drop in number of manufacturers from eight to three between 2002 and 2013 resulted in a price increase of over 600%.⁴⁰⁷ Another contributor is the business strategy of some companies to purchase older drugs without sufficient competitors and raise the price.⁴⁰⁸ Martin Shkreli, who as CEO of Turing Pharmaceuticals raised the price of pyrimethamine (Daraprim) from \$13.50 a pill to \$750 a pill in 2015, made it clear that his intentions were purely financial.⁴⁰⁹ In another case, GlaxoSmithKline sold its rights to the antiparasitic albendazole (FDA-approved in 1996) to Amedra Pharmaceuticals in October 2010. Without generic competition due to the small size of the market size for this antiparasitic drug, Amedra raised by the price from \$5.92 per dose by 2013 to \$119.58 per dose by 2013.⁴¹⁰

402. GENERIC COMPETITION AND DRUG PRICES, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm> (last visited Apr. 9, 2019).

403. Dave et al., *supra* note 401, at 2597.

404. Yuting Zhang et al., *Access to and Use of \$4 Generic Programs in Medicare*, 27 J. GEN. INTERNAL MED. 1251, 1251-52 (2012).

405. Chintan V. Dave et al., *High Generic Drug Prices and Market Competition: A Retrospective Cohort Study*, 167 ANNALS INTERNAL MED. 145, 149 (2017).

406. Chintan V. Dave et al., *Predictors of Drug Shortages and Association with Generic Drug Prices: A Retrospective Cohort Study*, 21 VALUE IN HEALTH 1286, 1289 (2018).

407. Jonathan D. Alpern et al., *High-Cost Generic Drugs—Implications for Patients and Policymakers*, 371 NEW ENG. J. MED. 1859, 1860 (2014).

408. Alfred B. Engelberg et al., *Addressing Generic Drug Unaffordability And Shortages By Globalizing The Market For Old Drugs*, HEALTH AFF. BLOG (Feb. 23, 2016), <https://www.healthaffairs.org/doi/10.1377/hblog20160223.053266/full>.

409. Carolyn Y. Johnson, *What Happened to the \$750 Pill that Catapulted Martin Shkreli to Infamy*, WASH. POST (Aug. 1, 2017), <https://www.washingtonpost.com/news/wonk/wp/2017/08/01/what-happened-to-the-750-pill-that-catapulted-pharma-bro-martin-shkreli-to-infamy>.

410. Jonathan D. Alpern et al., *High-Cost Generic Drugs—Implications for Patients and Policymakers*, 371 NEW ENG. J. MED. 1859, 1860 (2014).

Shortages of generic drugs can also lead to increasing prices.⁴¹¹ Such shortages are often multifactorial: supply chains and manufacturing processes can be disrupted, and companies may go out of business; each of these can leave a vacuum in the market for certain drugs. Some have blamed generic manufacturer market exits on increased FDA reviews of generic drug manufacturing facilities.⁴¹² Exceptions have also been made for importing raw materials, including those derived from plants, in response to drug shortages.⁴¹³ With the incidence and prevalence of drug shortages reaching record levels in the past several years, some policymakers have proposed more flexible approaches to importing drugs that facilitate competition in response to shortages while allowing time for competitors to enter the market and stabilize domestic supply.⁴¹⁴

Other programs may also interfere with generic competition. The FDA's Unapproved Drugs Initiative rewarded manufacturers for formally evaluating drugs that had never been approved by the FDA because they pre-date the 1938 Food, Drug, and Cosmetic Act.⁴¹⁵ One example of such a drug, widely available on the market and sold at inexpensive prices, is colchicine, based on an active ingredient that was first used to treat gout in ancient Greece over 3000 years ago. After a small trial in 2009,⁴¹⁶ Takeda Pharmaceuticals earned 3 years of market exclusivity and the FDA forced other colchicine manufacturers off the market. Takeda sold the brand-name version, Colcrys, for 50-times the

411. Dave et al., *Predictors of Drug Shortages*, *supra* note 406, at 1286; Inmaculada Hernandez et al., *Changes in Drug Pricing After Drug Shortages in the United States*, 170 *ANNALS INTERNAL MEDICINE* 74, 74-75 (2018).

412. C. Lee Ventola, *The Drug Shortage Crisis in the United States: Causes, Impact, and Management Strategies*, 36 *PHARMACY & THERAPEUTICS* 740, 741, 753 (2011); Robert King, *FDA Partly to Blame in EpiPen Price Debacle*, *WASH. EXAMINER* (Aug. 27, 2016), <https://www.washingtonexaminer.com/fda-partly-to-blame-in-epipen-price-debacle>.

413. Eric Palmer, *To Avoid Shortages, FDA Allows Imports from 8 Drug Plants Banned for Quality Shortfalls*, *FIERCEPHARMA* (Jul. 25, 2016), <http://www.fiercepharma.com/manufacturing/fda-allows-imports-from-8-banned-drug-plants-to-avoid-shortages>.

414. See Thomas J. Bollyky & Aaron S. Kesselheim, *Can Drug Importation Address High Generic Drug Prices?* 1-28 (The Brookings Inst., Hutchins Center Working Paper No. 29, 2017), https://www.brookings.edu/wp-content/uploads/2017/05/wp29_bollykykesselheim_drugimportation.pdf.

415. Ravi Gupta et al., *The FDA Unapproved Drugs Initiative: An Observational Study of the Consequences for Drug Prices and Shortages in the United States*, 23 *J. MANAGED CARE & SPECIALTY PHARMACY* 1066, 1074 (2017); Alexander Nasr et al., *Unapproved Drugs in the United States and the Food and Drug Administration*, 28 *ADVANCED THERAPY* 842, 843, 845 (2011); FDA, *UNAPPROVED DRUGS INITIATIVE*, "UNAPPROVED DRUGS INITIATIVE," <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm>.

416. Aaron S. Kesselheim et al., *Reductions in Use of Colchicine after FDA Enforcement of Market Exclusivity in a Commercially Insured Population*, 30 *J. GEN. INTERNAL MED.* 1633, 1633 (2015).

price (\$4.85/pill vs. \$0.09/pill) of its generic predecessor.⁴¹⁷ Similar episodes also happened with the anti-malarial quinine.⁴¹⁸

After the price of a generic drug spikes due to a decrease in competition, it may stay high because potential new entrants into the market need time to test products and receive FDA approval. Generic drug review times are slower than innovator drug review times and account in many instances for the inability of a generic manufacturer to quickly step in and make a more affordable version of a generic drug that is either expensive (e.g., pyrimethamine) or in shortage (e.g., many generic oncology drugs).⁴¹⁹ In 2014, the average ANDA review time for the FDA was forty-two months, compared to twelve months for an NDA.⁴²⁰ The generic drug backlog started to clear once the FDA began collecting user fees for generic drug applications under the Generic Drug User Fee Amendments Act of 2012. FDA review times for generic drugs have since fallen to an average of about ten months.⁴²¹ The Office of Generic Drugs within the FDA is also allowed to accelerate ANDA review to resolve drug shortages or insufficient competition, especially if they are the first generic version of a drug to enter the market or in cases where three or fewer manufacturers produce a given drug.⁴²²

D. Overseas Manufacturing

The United States is the largest pharmaceutical importer in the world; 40% of finished drugs and 80% of active pharmaceutical ingredients are imported from abroad.⁴²³ The U.S. pharmaceutical trade deficit is currently running at

417. Aaron S. Kesselheim & Daniel H. Solomon, *Incentives for Drug Development—The Curious Case of Colchicine*, 362 NEW ENG. J. MED. 2045, 2046 (2010).

418. Harris Meyer, *The High Price of FDA Approval*, KAISER HEALTH NEWS (Dec. 29, 2009), <http://khn.org/news/fda-approval>.

419. Jing Luo et al., *Regulatory Solutions to the Problem of High Generic Drug Costs*, 2 OPEN F. INFECTIOUS DISEASES 1, 1 (2015).

420. DEP'T. OF HEALTH & HUM. SERVS., UNDERSTANDING RECENT TRENDS IN GENERIC DRUG PRICES 9 (2016); FDA, CDER APPROVAL TIMES FOR PRIORITY AND STANDARD NDAS AND BLAS 1 (2016), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/UCM540942.pdf>.

421. FOOD & DRUG ADMIN, FY2017 PERFORMANCE REPORT TO CONGRESS FOR THE GENERIC DRUG USER FEE AMENDMENTS 18 (2017); FDA, "REAL-TIME REVIEW OF DRUG APPLICATIONS IS NOW A REALITY" (Sept. 20, 2018), <https://www.fda.gov/drugs/real-time-review-drug-applications-now-reality-september-20-2018-issue>.

422. FDA, ANDAS: PRE-SUBMISSION OF FACILITY INFORMATION RELATED TO PRIORITIZED GENERIC DRUG APPLICATIONS (PRE-SUBMISSION FACILITY CORRESPONDENCE) GUIDANCE FOR INDUSTRY 19 n.5 (2017). FDA, FDA TACKLES DRUG COMPETITION TO IMPROVE PATIENT ACCESS (June 27, 2017), <https://www.fda.gov/news-events/press-announcements/fda-tackles-drug-competition-improve-patient-access>.

423. INT'L TRADE ADMIN., 2016 TOP MARKET REPORT PHARMACEUTICALS 9 n.20; 4 (2016).

about \$52 billion (drug exports in the United States have not grown since 2009). These current realities emphasize the importance of ensuring a safe pharmaceutical supply chain.

However, policymakers have expressed concern about the FDA's resources and capacity to conduct inspections abroad to assure compliance with good manufacturing practices.⁴²⁴ In widely publicized instances, certain generic manufacturers have been cited for substandard manufacturing practices.⁴²⁵ Though a recent series of articles in Bloomberg points to safety concerns with overseas generic drug manufacturers and points to a decline in both foreign and U.S. inspections,⁴²⁶ the FDA has challenged this account, showing evidence that the number of facility inspections have increased, not fallen.⁴²⁷

Despite occasional reports of substandard manufacturing that require investigation, the US prescription drug market is remarkably free of poor quality of counterfeit products, particularly considering the United States' substantial pharmaceutical trade deficit. To address concerns, the FDA has sought to enhance global harmonization with other reviews conducted by other countries' drug regulators and the World Health Organization, as well as to increase its on-site capacity in key areas like India and China.

CONCLUSION

The U.S. pharmaceutical industry has evolved considerably in the last century. In the late 1800s and early 1900s, "snake oil" remedies containing poisonous substances could be marketed without any government oversight. Now, the FDA spends considerable time and resources ensuring that the benefits of a given drug outweigh known risks prior to entering the marketplace, and engaging in ongoing safety surveillance that continues for years after FDA approval. Though a robust generic drug market emerged out of the Hatch-Waxman Act of 1984, legislation in the last thirty-five years reflects a struggle on the part of Congress to balance access and affordability with the intellectual property protections covering innovative products that permit manufacturers to charge exorbitant prices. In the current era, brand-name manufacturers can set drug list prices at what the market will bear and extend market exclusivity and profitability by engaging in a variety of questionable

424. FDA, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS, HOUSE COMMITTEE ON ENERGY AND COMMERCE (2007), <https://babel.hathitrust.org/cgi/pt?id=pst.000065519790;view=1up;seq=3>.

425. Atholl Johnston & David W. Holt, *Substandard Drugs: A Potential Crisis for Public Health*, 78 BRIT. J. CLINICAL PHARMACOLOGY 218, 218 (2014).

426. Anna Edney, *America's Love Affair with Cheap Drugs Has a Hidden Cost*, BLOOMBERG (Jan. 29, 2019), <https://www.bloomberg.com/news/features/2019-01-29/america-s-love-affair-with-cheap-drugs-has-a-hidden-cost>.

427. Scott Gottlieb (@SGottliebFDA), TWITTER (Feb. 2, 2019, 10:34 AM), <https://twitter.com/SGottliebFDA/status/1091751751890468866>.

practices. As payors and consumers are forced to cover the rising costs of prescription drugs, we may see substantial changes in the way prescription drugs are developed and priced, driven by new legislative and regulatory policymaking.