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How the Government Created and Sustains the Private Pharmaceutical Industry

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HOW THE GOVERNMENT CREATED AND SUSTAINS THE PRIVATE PHARMACEUTICAL INDUSTRY

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I. INTRODUCTION

The private pharmaceutical industry is perennially one of the most profitable in the United States.[1] Its success is built on a cascade of products, some of which generate billions of dollars in sales each year.[2] New ones continually enter the market to replenish the supply.

Companies that ultimately market new drugs are visible to all. Their partners in research and clinical testing are known in the industry and throughout the investment community. What is not as readily apparent is the partner that creates the foundation for the entire drug development process. That is the government.[3]

New drugs emerge from many different sources. Some come from research that applies basic biological knowledge.[4] Some emerge from trial

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1. Uwe E. Reinhardt, *Perspectives on the Pharmaceutical Industry*, HEALTH AFF., Sept. – Oct. 2001, at 142-43.

2. *See, e.g.*, PHARM. RESEARCH & MFRS. OF AM., PHARMACEUTICAL INDUSTRY PROFILE 2010, at 50 tbl.8 (2010).

3. Iain M. Cockburn & Rebecca M. Henderson, *Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery*, 46 J. INDUS. ECON. 157, 160 (1998); Benjamin Zycher et al., *Private Sector Contributions to Pharmaceutical Science: Thirty-Five Summary Case Histories*, 17 AM. J. THERAPEUTICS 101, 103 (2010).

4. *See* PHARM. RESEARCH & MFRS. OF AM., *supra* note 2, at 33.

and error.[5] Others materialize from serendipity when they are least expected.[6]

It is a long and expensive path from the initial conjecture that a substance may have clinical potential to its ultimate entry into the market.[7] The path has countless twists and turns, and many journeys do not succeed.[8] When one does, a single player rarely travels the entire road alone.[9] Whatever the initial source of discovery, multiple partners usually join the effort, and they come from both the public and private spheres.[10]

Few would dispute the value of government-funded research as the foundation of drug discovery. Even the most ardent admirers of private industry innovation concede the importance of the government in promoting the underlying science on which it rests.[11] Debates may rage over the relative amount of credit that each side deserves, but not over the necessity of both sectors to the advancement of pharmaceutical science.

Most of the drugs in wide use today resulted from such public-private collaborations. Of the 21 drugs with the highest therapeutic impact, 14 stemmed directly from an enabling discovery that the government had supported.[12] Often, public and private research continues to interact even after a new drug therapy has reached the market.[13] Such continuing interchanges have produced major breakthroughs, for example better understanding of the mechanism of action of Azidothymidine (AZT) as a treatment for HIV infection.[14]

However, the public-private partnership does not end with a handoff from government-backed basic scientists to applied investigators in corporate settings. The public sector contributes to drug development throughout the lifecycle of new drugs in many ways.[15] Perhaps most significantly, it creates vast markets for drugs through public health

5. Stefan Thomke et al., *Modes of Experimentation: An Innovation Process - and Competitive - Variable*, 27 RES. POL'Y 315, 324 (1998).

6. Thomas A. Ban, *The Role of Serendipity in Drug Discovery*, 8 DIALOGUES CLINICAL NEUROSCIENCE 335, 342 (2006).

7. PHARM. RESEARCH & MFRS. OF AM., *supra* note 2, at 27.

8. *Id.* at 27-28.

9. *See id.* at 33.

10. *See id.*

11. Zycher et al., *supra* note 3, at 102. In this study, the authors seek to demonstrate the value of industry research and development in bringing important new drugs to patients. *Id.* at 105. They begin their analysis by observing, "the importance of government-funded research, particularly in terms of the science of disease processes and applications to pharmacologic advances, is not in dispute." *Id.* at 103.

12. Zycher et al., *supra* note 3, at 105, 116.

13. *See* Cockburn & Henderson, *supra* note 3, at 160.

14. Zycher et al., *supra* note 3, at 112.

15. Cockburn & Henderson, *supra* note 3, at 160.

insurance programs. Medicare, which insures the elderly, spends over $55 billion a year on outpatient prescriptions, and over $10 billion on drugs administered by physicians.[16] Medicaid, which insures the poor, spends over $26 billion a year.[17] The government also purchases drugs for veterans through the Veterans Health Service and through the Department of Defense for military personnel and their dependents.[18]

The government also shapes the pharmaceutical industry through regulation. The primary agency involved is the Food and Drug Administration (FDA), which serves as a gatekeeper to determine which drugs may reach the market.[19] To pass through the gate, new products must undergo years of clinical testing that assess safety and effectiveness.[20] After approval, the FDA continues to monitor drugs for safety and to impose restrictions on marketing and promotion.[21] The FDA-imposed testing process accounts for the lion's share of the cost of drug development and sets parameters for the kinds of drugs that ultimately reach patients.[22] While manufacturers may complain about bureaucratic inefficiency and delays on the agency's part, this vetting process is largely responsible for the public's confidence in their products.[23]

Beyond the FDA, patent laws, administered by the United States Patent and Trademark Office (USPTO), circumscribe the commercialization and marketing process.[24] Patent rules determine the nature and length of the

16. MEDICARE PAYMENT ADVISORY COMM'N, A DATA BOOK, HEALTHCARE SPENDING AND THE MEDICARE PROGRAM 169 (2010), *available at* www.medpac.gov/documents/jun10databook entirereport.pdf; *see* KAISER FAMILY FOUND., MEDICARE SPENDING AND FINANCING FACT SHEET 1 (2010), *available at* http://www.kff.org/medicare/upload/7305-05.pdf [hereinafter KAISER FAMILY FOUND., MEDICARE SPENDING].

17. JOHN HOLAHAN ET AL., KAISER FAMILY FOUND., MEDICAID SPENDING GROWTH OVER THE LAST DECADE AND THE GREAT RECESSION, 2000-2009 at 8, 10 (2011), *available at* www.kff.org/medicaid/upload/8152.pdf.

18. CONG. BUDGET OFFICE, PUB. NO. 3016, THE HEALTH CARE SYSTEM FOR VETERANS: AN INTERIM REPORT 1 (2007); *TRICARE Facts and Figures*, TRICARE (March 2012), http://www.tricare.mil/pressroom/press_facts.aspx.

19. SUSAN THAUL, CONG. RESEARCH SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 1 (2012).

20. *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD & DRUG ADMIN. (May 1, 2012), http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm.

21. THAUL, *supra* note 19, at 8.

22. *See* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 167 (2003).

23. ROBERT I. FIELD, HEALTH CARE REGULATION IN AMERICA: COMPLEXITY, CONFRONTATION, AND COMPROMISE 139 (2007); Dale H. Gieringer, *The Safety and Efficacy of New Drug Approval*, 5 CATO J. 177, 177, 178 (1985).

24. *See* F.M. Scherer, *The Pharmaceutical Industry – Prices and Progress*, 351 NEW ENG. J. MED. 927, 927-28 (2004).

monopoly granted to new drugs, which is what makes them profitable to develop.[25] These rules are supplemented by a number of related laws that further refine the contours of the pharmaceutical market. These include the Drug Price Competition and Patent Term Restoration Act,[26] commonly known as the Hatch-Waxman Act, which structures the market for generic competition, and the Food and Drug Administration Modernization Act (FDAMA),[27] which extends monopoly protection for drugs that are tested on children.

II. AMERICA'S ROBUST DRUG COMPANIES

A. Perennial Profitability

Over the past 20 years, no American industry has outperformed pharmaceutical manufacturing in terms of profitability. According to the most widely used measures, drug companies earned three times the median of all Fortune 500 companies in 2004 and over five times the median in 2001.[28] Between 1995 and 2002, pharmaceutical manufacturing was the most profitable industry in the United States, and since then it has remained in the top three every year.[29] The rate of return on investment consistently hovers near 20%, a figure that most other industries can only dream of.[30]

Sales of prescription drugs in the United States now exceed $300 billion a year.[31] Even during the recession year of 2009, sales remained robust, growing at a rate of 5.1% from the year before.[32] Global sales for 2009

25. *Id.*

26. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 35, 42 U.S.C. (2006)).

27. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21, 26, 42 U.S.C. (2006)).

28. *Trends and Indicators in the Changing Health Care Marketplace*, KAISER FAMILY FOUND. (Feb. 8, 2006), http://www.kff.org/insurance/7031/ti2004-1-21.cfm.

29. MICHELE BOLDRIN & DAVID K. LEVINE, AGAINST INTELLECTUAL MONOPOLY 256 (2008); KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS 4 (2010), *available at* http://www.kff.org/rxdrugs/upload/3057-08.pdf [hereinafter KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS].

30. Reinhardt, *supra* note 1, at 136, 142.

31. IMS INST. FOR HEALTHCARE INFORMATICS, THE USE OF MEDICINES IN THE UNITED STATES: REVIEW OF 2010, at 4 (2011), *available at* http://www.imshealth.com/deployedfiles/imshealth/Global/Content/IMS%20Institute/Static%20File/IHII_UseOfMed_report.pdf.

32. *Id.*

stood at $837 billion after rising 7% from a year earlier.[33] Both domestically and globally, these rates continue to accelerate.[34]

B. The Financial Engine: Research and Development

Several factors account for the pharmaceutical industry's consistent good fortune.[35] For one, demand for health-enhancing and life-saving products will never diminish, so the industry's output will always be needed.[36] For another, most consumers today have assistance from third parties in paying for pharmaceutical products through some form of insurance, either public or private.[37]

The pharmaceutical industry is also able to charge high prices for many of its products because they are insulated from market competition through patents.[38] While patents do not last indefinitely, they, along with various other legal protections, offer most prescription drugs at least 10 years of market exclusivity after they first reach consumers and often more.[39]

The exclusive sale of life-saving products is certainly a recipe for financial success, but only if one more ingredient is present. As patents expire, competitive pricing by manufacturers of generic copies drives down profit margins, so a steady supply of new drugs is needed.[40] The industry must devote a tremendous amount of its attention and resources to that end. To maintain profitability, a steady supply of fresh products must continually flow through each company's "pipeline."[41]

33. *Biopharma Forecasts & Trends*, IMS INST. (2012), http://www.imshealth.com/portal/site/ims/menuitem.d248e29c86589c9c30e81c033208c22a/?vgnextoid=4b8c410b6c718210VgnVCM100000ed152ca2RCRD&vgnextfmt=default.

34. *Id.*

35. The appropriate accounting for pharmaceutical profitability is somewhat controversial. Some analysts believe that the treatment of research and development costs in standard assessments is incorrect. Scherer, *supra* note 24, at 929. They contend that it should be treated as an investment subject to depreciation rather than an expense. *Id.* This approach generates much lower rates of profits in comparison to assets. *Id.* Nevertheless, the resulting profitability is still consistently higher than the average for all American industries. *Id.*

36. *See* NNE Pharmaplan, *Biopharmaceuticals: Entering a New World*, ANGLE, April 2012, at 5, 39. "As the global population grows and life expectancy rises, biopharmaceuticals are in ever greater demand for the treatment of life-threatening and chronic diseases." *Id.* at 5.

37. *See* KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS, *supra* note 29, at 5.

38. *See* Scherer, *supra* note 24, at 927.

39. *Id.*

40. *Id.* at 929.

41. ROY LEVY, THE PHARMACEUTICAL INDUSTRY: A DISCUSSION OF COMPETITIVE AND ANTITRUST ISSUES IN AN ENVIRONMENT OF CHANGE, BUREAU OF ECON. STAFF REPORT, FED. TRADE COMM'N (March 1999).

The never-ending search for new products has shaped the pharmaceutical industry into the most research-intensive in the United States.[42] It devotes more private resources to scientific investigation than any other.[43] In 2002, this investment equaled 18% of sales, which is roughly five times the average for American manufacturing firms.[44] Since 1985, this percentage has been higher even than that devoted by the computer industry.[45]

The exact magnitude of pharmaceutical research and development spending is subject to some dispute. The industry's trade association, the Pharmaceutical Research and Manufacturers of America (PhRMA) uses a broad definition that includes spending on post-market monitoring of drugs after their final approval by the FDA.[46] By this measure, research spending grew from $6 billion to $39 billion between 1980 and 2004 in constant 2005 dollars, reflecting an average rate of increase of about 8%.[47] PhRMA puts the 2009 figure at $65.3 billion.[48] The National Science Foundation (NSF) calculated the value of industry research at the premarket phases only and found an increase from $5.5 billion to $17 billion over the same period, for an average rate of growth of 5%.[49] Nevertheless, under either analysis, the industry has steadily and dramatically expanded its commitment to research over a considerable period of time.

Of course, not all of this research activity actually creates new drugs that are truly innovative. About two-thirds of the new drug applications (NDAs) submitted to the FDA each year do not involve a new molecular entity (NME).[50] Instead, they represent reformulations or minor modifications of existing drugs or requests for approval of new uses.[51] Drugs involving reformulations or incremental modifications of existing modifications are commonly known as "me-too" drugs, as they follow an established therapeutic approach.[52] In most years, the FDA approves only about 20 drugs that are based on new NMEs.[53]

42. Scherer, *supra* note 24, at 927.

43. CONG. BUDGET OFFICE, PUB. NO. 2589, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 7 (2006) [hereinafter CONG. BUDGET OFFICE, R&D].

44. *See id.* at 10 fig.2-2.

45. *Id.*

46. PHARM. RESEARCH & MFRS. OF AM., *supra* note 2, at 41.

47. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 7.

48. PHARM. RESEARCH & MFRS. OF AM., *supra* note 2, at b.

49. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 7.

50. *Id.* at 2.

51. *Id.* at 14-15.

52. *Id.* at 2.

53. *Id.* at 3.

However, regardless of the originality of the drugs being introduced, the steady flow of new products is a hallmark of the pharmaceutical industry. One can debate how much clinical value is actually contributed when new drugs mimic existing ones, but it is undeniable that the industry as we know it today thrives on a massive research and development apparatus. It is in this regard that the government provides it with the biggest boost.

III. THE CORNERSTONE OF PUBLIC BIOMEDICAL RESEARCH: NIH

How does the industry find the new drugs it needs to refresh its inventory? For two-thirds of its products, the answer is easy as they are me-too drugs based on established products.[54] For the one-third of new drugs that represents true innovation, the answer is more complex. These are medications that are truly new and that emerge from advances in scientific knowledge.[55] This is where the implicit partnership with the government is most essential.

A. A Mission to Underwrite Biomedical Science

The government's foundational role in promoting biomedical research is administered primarily by the National Institutes of Health (NIH). This massive agency, which is a component of the United States Department of Health and Human Services, spends about $30 billion a year to enhance the fundamental understanding of biology and medicine.[56] That amount has more than doubled since the mid-1990s.[57] Most of it is devoted to basic science that seeks to decipher underlying physiological mechanisms — the raw fuel that private companies refine into finished commercial products.[58]

The division of research roles between industry and government is not a simple split between applied and basic science. NIH performs some applied clinical studies of new drugs, and private industry conducts some basic research.[59] The relationship between the private and public spheres is further blurred by a range of other government programs that promote the

54. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 2.

55. *Id.* at 7.

56. *NIH Almanac, Appropriations (Section 2)*, NAT'L INSTS. OF HEALTH (March 6, 2012), http://www.nih.gov/about/almanac/appropriations/part2.htm [hereinafter *NIH Almanac*].

57. *Id.*

58. *Department of Health and Human Services, National Institutes of Health Fiscal Year 2013 Budget Request: Hearing Before the H. Subcomm. on Labor – HHS – Education Appropriations*, 112th Cong. 4-5 (2012) (statement of Francis S. Collins, Director, National Institutes of Health).

59. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 3.

translation of NIH-funded research into commercial uses.[60] However, in all of these endeavors, the two sectors follow a similar pattern of partnership to produce new medicines.[61]

The importance of government-sponsored research to pharmaceutical industry vitality cannot be overstated. One analysis estimated that every 1% increase in public research funding produces an increase of between 2 and 2.4% in the number of commercially available new compounds.[62] Another projected the rate of return from public funding of biomedical research at up to 30% a year.[63] Without question, government-funded science is an essential ingredient underlying the industry's business model.

B. NIH's Growth from Humble Origins

The huge scientific enterprise that NIH represents today began as a modest endeavor in the late nineteenth century in Staten Island, New York.[64] Dr. Joseph J. Kinyoun set up a laboratory in a marine hospital there in 1887 to study bacteria that cause common infectious diseases.[65] He succeeded in identifying the organism that causes cholera, the cholera bacillus, which aided physicians in diagnosing suspicious cases of this deadly disease.[66] Successes such as this led the government to move his laboratory in 1891 to Washington, D.C. and to give it a new name, the Hygienic Laboratory.[67] Ten years later, Congress authorized $35,000 for a new building to house it.[68]

The Hygienic Laboratory gained new responsibilities and prominence in 1902, when Congress created a Division of Pathology and Bacteriology within the federal Marine Hospital Service to house its research.[69] At that time, the laboratory also added Ph.D.-trained researchers to the physicians in its workforce.[70] Among its new responsibilities was setting standards and

60. *See* ANDREW A. TOOLE, STANFORD INST. FOR ECON. POLICY RESEARCH, THE IMPACT OF PUBLIC BASIC RESEARCH ON INDUSTRIAL INNOVATION: EVIDENCE FROM THE PHARMACEUTICAL INDUSTRY 9 (2000).

61. *See id.* at 12-13.

62. *Id.* at 5.

63. Iain M. Cockburn & Rebecca M. Henderson, *Publicly Funded Science and the Productivity of the Pharmaceutical Industry*, *in* 1 INNOVATION POLICY AND THE ECONOMY 1, 28 (Adam B. Jaffe et al. eds., 2001).

64. Victoria A. Harden, *A Short History of the National Institutes of Health*, NAT'L INSTS. OF HEALTH OFFICE OF NIH HISTORY (2005), http://history.nih.gov/exhibits/history/index.html.

65. *Id.*

66. *Id.*

67. *Id.*

68. *Id.*

69. Harden, *supra* note 64.

70. *Id.*

issuing licenses for the manufacture of vaccines and antitoxins by private companies, a role that was included in the Biologics Control Act, passed that year.[71] This responsibility was eventually transferred to the FDA in 1972.[72] Along with this new regulatory authority came an expanded mission of research to support it.[73]

Another round of important scientific discoveries emerged from the laboratory in the years leading up to World War I.[74] These included such practical findings as the link between pellagra and a dietary deficiency and between unsanitary conditions around military bases and disease outbreaks.[75] In recognition of its growing contributions, scientists who worked in the laboratory were accepted for the first time as members of the executive branch of government.[76] In 1912, the agency housing the laboratory was renamed the Public Health Service.[77]

As the value of biomedical science became increasingly apparent, efforts were launched after the War to expand its reach.[78] Most notably, a group of scientists from a wartime agency, the Chemical War Service, sought industry funding to support research into applications of chemistry to medicine.[79] However, several years of trying yielded no success in attracting private sponsors.[80]

In 1926, the scientists gave up their quest to find funding in the private sector and turned to Congress, instead.[81] They found a champion in Senator Joseph E. Ransdell of Louisiana, who in 1930 successfully sponsored legislation to fund fellowships for basic research within the Hygienic Laboratory.[82] The Ransdell Act also changed the name of the laboratory to the National Institute of Health.[83] Initial funding was modest, but it marked the start of a new approach to the sponsorship of research under government auspices.[84] Funding grew significantly over the years along with

71. *Id.*
72. *Id.*
73. *Id.*
74. Harden, *supra* note 64.
75. FIELD, *supra* note 23, at 207.
76. VICTORIA A. HARDEN, INVENTING THE NIH: FEDERAL BIOMEDICAL RESEARCH POLICY, 1887-1937, at 3 (1986).
77. Harden, *supra* note 64.
78. *See* FIELD, *supra* note 23, at 207-08.
79. Harden, *supra* note 64.
80. *Id.*
81. *Id.*
82. Ransdell Act, Pub. L. No. 71-251, 46 Stat. 379 (1930) (codified as amended at 42 U.S.C. §§ 21, 22, 23a–23g (2006)).
83. Harden, *supra* note 64.
84. *Id.*

the Institute's mission, and the name was pluralized in 1948 to recognize a more diverse role.[85]

C. *Expansion into a Research Powerhouse*

NIH is organized today into 27 component institutes that focus on specific categories of diseases or types of therapy.[86] Each employs scientists in-house to work in government laboratories but spends most of its resources funding researchers outside of the government in universities and research institutes.[87] The model for this structure originated in 1937 with the establishment of the National Cancer Institute (NCI).[88] Originally organized as an independent agency, it was formally incorporated into NIH in 1944.[89]

The intramural research component of NIH's mission gained a major boost in 1940, when the agency opened its sprawling campus in Bethesda, Maryland.[90] The land was donated by Mr. and Mrs. Luke Wilson, and today it houses one of the largest collections of scientific research buildings in the world.[91] In 1953, a large hospital, the Warren Grant Magnuson Clinical Center, was added to the site.[92] When he dedicated the complex, President Franklin Roosevelt emphasized the significance of the enterprise to national security on the eve of America's entry into World War II. He observed: "We must recruit not only men and materials but also knowledge and science in the service of national strength and that is what we are doing here."[93]

If anyone doubted the value of biomedical science to military strength at the time, World War II would have removed any uncertainty. As one observed noted, the war effort "had mobilized a concerted government effort — unprecedented to date — in applying research to practical use."[94] America's success in the War owed a huge debt to a long list of medical

85. *See* FIELD, *supra* note 23, at 208.

86. *About NIH*, NAT'L INSTS. OF HEALTH (Aug. 7, 2012), http://www.nih.gov/about/ [hereinafter *About NIH*].

87. *NIH Budget*, NAT'L INSTS. OF HEALTH (March 1, 2012), http://www.nih.gov/about/budget.htm.

88. Harden, *supra* note 64.

89. *Id*.

90. *The NIH Almanac—Historical Data*, NAT'L INSTS. OF HEALTH (March 27, 2012), http://www.nih.gov/about/almanac/historical/chronology_of_events.htm.

91. Carla Garnett, *Last of 'Treetops,' Bldg. 15K Is Refurbished*, NAT'L INSTS. OF HEALTH RECORD (May 29, 2001), http://nihrecord.od.nih.gov/newsletters/05_29_2001/story01.htm.

92. Harden, *supra* note 64.

93. Franklin Delano Roosevelt, *The Dedication of the National Institutes of Health*, 36 CLINICAL RESEARCH 1, 1-2 (1988).

94. JUDITH ROBINSON, NOBLE CONSPIRATOR: FLORENCE S. MAHONEY AND THE RISE OF THE NATIONAL INSTITUTES OF HEALTH 59 (2001).

advances developed at that time, most of which continue to protect us today.[95]

The importance of these medical advances was not lost on the public or on politicians. As the War ended, NIH received significant new authority to maintain its research role.[96] Initially, it received responsibility for phasing out wartime research contracts with universities, but Congress soon changed course and decided that many of these arrangements should remain in place.[97] The agency continued to administer them, and it received additional funding and staff to pursue this mission.[98] The Public Health Service Act of 1944, which had merged NCI into NIH, provided for the creation of additional component institutes, and it set in motion a series of dramatic budget increases that have continued ever since.[99] An NIH budget of $4 million in 1947 grew to $100 million in 1957, to $1 billion in 1974, to more than $27 billion in 2004, and to $30 million in 2009.[100]

D. NIH as the Backbone of Biomedical Science

From the perspective of public policy, the most significant aspect of the steady NIH budget increases is the portion that is directed to private researchers. About 80% of the agency's budget supports studies at universities, research institutes, and similar organizations.[101] Scientists in these settings propose the actual structure of the studies they wish to conduct and the research questions they will pursue.[102] The agency then constitutes committees of experts from outside of government to determine which of these proposals merit funding.[103] This arrangement shapes the huge research enterprise that the agency supports as a public-private partnership on a massive scale. In the words of one observer: "Never in the nation's history had public funds in such amounts been placed at the disposal of individuals working in support of their own objectives outside the framework of federal institutions."[104]

Over the years since World War II, the nation has looked to NIH time and time again as the first line of attack to address pressing health needs. In

95. FIELD, *supra* note 23, at 209.

96. *Id.*

97. *Id.*

98. *Id.*

99. Public Health Service Act of 1944, Pub. L. No. 78-410, § 401, 58 Stat. 682, 707 (codified as amended at 42 U.S.C. § 281 (2006)); FIELD, *supra* note 23, at 210.

100. FIELD, *supra* note 23, at 210; *NIH Almanac*, *supra* note 56.

101. *About NIH*, *supra* note 86.

102. FIELD, *supra* note 23, at 205.

103. *Id.* at 225.

104. James A. Shannon, *Advancement of Medical Research: A Twenty-Year View of the Role of the National Institutes of Health*, 42 J. MED. EDUC. 97, 103 (1967).

1971, President Richard Nixon launched a "war on cancer" by asking Congress to expand funding for NCI.[105] In the early 1980s, advocates for patients with AIDS lobbied Congress to increase support for NIH research into the disease's cause and potential treatments.[106] In the late 1990s, advocates for patients with Parkinson's Disease successfully lobbied for additional NIH funding for research into that condition.[107]

As the nature of medicine has changed, the focus of NIH-sponsored research has evolved along with it. In 1992, the agency added the National Center for Complimentary and Alternative Medicine, and in 1993, the National Center on Minority Health and Health Disparities.[108] With all of these changes in funding priorities and focus, the goal of Congress and the desire of much of the public has been to keep the government in the lead in moving American medicine forward.[109]

The influence of NIH on biomedical science in America extends well beyond its support for individual studies to a role in shaping a key foundation of the research enterprise. That is building and maintaining the pipeline of new scientists. The agency funds the education of most doctoral students in biomedical sciences along with additional postdoctoral training that many of them receive.[110] Before NIH provided this support, Ph.D.s in biomedical science were relatively rare.[111] Today, those holding these degrees form the workforce that conducts most research that leads to new pharmaceutical products. In the words of one observer: ". . . there is no question that the American pharmaceutical and biotechnology industries (which lead the world) could not exist, let alone thrive, without those thousands of trained people."[112]

E. NIH as the Instigator of Drug Development Collaborations

When a finding in basic science holds therapeutic promise, NIH does not have to wait passively for a private company to express interest. It is empowered to proactively seek out a corporate partner to work in

105. *See* National Cancer Act of 1971, 42 U.S.C. § 201 (2006); *see also* FIELD, *supra* note 23, at 211.

106. The history of the AIDS epidemic is chronicled in RANDY SHILTS, AND THE BAND PLAYED ON: POLITICS, PEOPLE AND THE AIDS EPIDEMIC (1987).

107. Morris K. Udall Parkinson's Disease Research Act of 1997, Pub. L. No. 105-78, 111 Stat 506 (codified as amended at 42 U.S.C. 284 (2006)).

108. *National Center for Complementary and Alternative Medicine*, NAT'L INSTS. OF HEALTH (April 10, 2012), http://www.nih.gov/about/almanac/organization/NCCAM.htm.

109. *About NIH*, *supra* note 86.

110. Richard B. Thompson, *Foundations for Blockbuster Drugs in Federally Sponsored Research*, 15 J. FED'N AM. SOCIETIES FOR EXPERIMENTAL BIOLOGY 1671, 1673 (2001).

111. *Id.*

112. *Id.*

partnership to bring a product to market.[113] This explicit path to collaborative drug development has led to the creation of numerous important medications, some of which have revolutionized medical practice and brought sizable financial rewards to the private partners involved. Among recent successes under these laws are the development of Thyrogen, a form of thyroid stimulating hormone commercialized by Genzyme, Prezista, a treatment for HIV infection commercialized by Tibotec, and Gardasil, a vaccine against the human papilloma virus which can cause cervical cancer that is sold by Merck.[114]

Congress facilitated the process of forming explicit government-industry collaborations with several legislative enactments. It first focused on this area in 1980.[115] A major impetus was the ruling by the Supreme Court that year that permitted the award of patents for artificially engineered life forms in the case of Diamond v. Chakrabarty.[116] That decision formed the legal foundation for the rise of the biotechnology industry by offering investors a route to profit from new discoveries.[117]

Biotechnology companies seek to commercialize the fruits of academic, government and industry research, however the task of coordinating the contributions of each of these sectors can be daunting.[118] They function in separate worlds with vastly different modes of operation. As the nascent industry began to take shape, barriers between them threatened to disrupt potential synergies that could help it to take off.[119]

Congress used several strategies to encourage the growth of the biotechnology industry and the commercialization of biomedical discoveries.

113. Steven M. Ferguson, *Products, Partners & Public Health: Transfer of Biomedical Technologies from the U.S. Government*, 5 J. BIOLAW & BUS., no. 2, 2002 at 35, 35.

114. Jack Spiegel, *NIH Technology Transfer: An Overview*, NAT'L INSTS. OF HEALTH (Feb. 19, 2008), http://www.nihtraining.com/cc/ippcr/current/downloads/Spiegel%202-19-08.pdf.

115. In 1980, Congress passed the Bayh-Dole Act. Patent and Trademark Laws Amendment (Bayh-Dole) Act of 1980, Pub. L. No. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. § 200-212 (2006)). The "law strengthened patent protections for inventions that result from research conducted with NIH funding in order to encourage the development of practical applications." FIELD, *supra* note 23, at 213-14.

116. Diamond v. Chakrabarty, 447 U.S. 303, 309-10 (1980).

117. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 9.

118. *See* Gina A. Kuhlman, *Alliances for the Future: Cultivating a Cooperative Environment for Biotech Success*, 11 BERKELEY TECH. L.J. 312, 312, 314 (1996).

119. *See* Walter W. Powell et al., *Interorganizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology*, 41 ADMIN. SCI. Q. 116, 118 (1996).

A simple one was to offer tax credits to companies that conduct research.[120] These have proven quite valuable to industry over time.[121]

A more complex strategy with more far-reaching impact was to create a framework for building explicit partnerships between the federal government and industry. A collection of laws implement strong incentives for companies and universities to collaborate with the government to bring scientific advances to market. Of these, the Patent and Trademark Law Amendment Act of 1980, commonly known as the Bayh-Dole Act, is the most important.[122] It gives institutions that receive NIH research grants the right to patent inventions that flow from the fruits of their investigations.[123] The goal is to give universities an incentive to attempt to commercialize research conducted under their auspices.[124]

Despite this incentive, private firms are often reluctant to invest in the initial basic research that is needed before actual product development can begin.[125] To address this gap, Congress developed a mechanism to formalize arrangements between government agencies and private entities to work jointly on the commercialization of breakthrough technologies. This is accomplished through a type of understanding known as a Cooperative Research and Development Agreement (CRADA).[126] These are partnerships that allow for joint development with a negotiated set of contributions, responsibilities, and remuneration involving each party.[127]

CRADAs are based on a series of laws that Congress enacted during the 1980s to encourage the transfer of technology from government laboratories to private firms that can commercialize it.[128] The primary law is the Stevenson-Wydler Technology Innovation Act of 1980, which established

120. Kuhlman, *supra* note 118, at 333; *e.g.*, Patient Protection and Affordable Care Act, Pub. L. No. 111-148,124 Stat. 119, 877 (2010) (to be codified at 26 U.S.C. 48D (2006)) (providing a recent example of the government's support of the industry via tax subsidies).

121. *See* Kuhlman, *supra* note 118, at 333.

122. Patent and Trademark Laws Amendment (Bayh-Dole) Act of 1980, Pub. L. No. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. § 200-212 (2006)); see discussion in Robert I. Field, *Government as the Crucible for Free Market Health Care: Regulation, Reimbursement, and Reform*, 159 U. PA. L. REV. 1669, 1703 (2011) [hereinafter Field, *Government as the Crucible*].

123. Patent and Trademark Laws Amendment Act of 1980 § 200.

124. *Id.* Patents are occasionally used defensively to prevent competitors from manufacturing an invention while the inventor decides whether it is worthwhile to take it to market. To avoid such possible misuse of the Act's benefits, it contains a "march-in" provision that gives NIH the ability to circumvent a patent when a product is potentially life saving. That provision has been rarely used, but it remains a check on potential abuses. *Id.* at § 203.

125. *See* Kuhlman, *supra* note 118, at 316.

126. Field, *Government as the Crucible*, *supra* note 122, at 1703.

127. *See id.*

128. *Id.*

a set of offices to coordinate technology transfer within each federal agency that conducts research.[129] In NIH, the office is known as the Office of Technology Transfer.[130] An amendment to the law enacted in 1986 as part of the Technology Transfer Act mandated that the federal government actively seek opportunities to transfer technology to industry, academia, or state and local governments, rather than passively waiting for them to arise.[131] This mandate works in tandem with the Bayh-Dole Act, which permits private parties to obtain patent rights to the fruits of these efforts.[132]

Under a CRADA, the government and the private partner share costs in their joint research and development effort.[133] Both may contribute personnel, services and property, but only the private party may contribute money to avoid triggering federal procurement statutes.[134] The government can grant a license to manufacture and sell the ultimate product to the industry partner, or it can simply waive its right of ownership.[135] In selecting a private partner, the government gives preference to business units located in the United States that agree to manufacture any resulting products in the county.[136] To reassure companies concerned about trade secrets, confidential information developed under a CRADA can be protected by the government partner from public disclosure for up to five years.[137]

F. NIH's Role in Creating the Future of Medicine

More recently, NIH has taken an even more proactive role in advancing medicine by laying the foundation for the new era of genomics. The agency has worked on several fronts to clear a path for this new frontier in biomedical science. Its explicit goal is to promote a revolution in the understanding of human biology that will lead to products that can be

129. Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, 94 Stat. 2311 (codified as amended at 15 U.S.C. § 3701-14 (2006)); see discussion in Field, *Government as the Crucible*, *supra* note 122, at 1703.

130. *About NIH OTT*, NAT'L INSTS. OF HEALTH, OFFICE OF TECH. TRANSFER, http://www.ott.nih.gov/about_nih/about.aspx (last visited Sept. 17, 2012).

131. Federal Technology Transfer Act of 1986, Pub. L. No. 99-502, 100 Stat. 1785, 1787 (codified as amended at 15 U.S.C. 3710 (2006)); Field, *Government as the Crucible*, *supra* note 122, at 1703-04.

132. Patent and Trademark Laws Amendment (Bayh-Dole) Act of 1980, Pub. L. No. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. § 200-212 (2006)).

133. *See* 15 U.S.C. § 3710a(d)(1) (2006).

134. *Id.*

135. *Id.* § 3710a(b)(1), (2)(D).

136. *Id.* § 3710a(c)(4)(B).

137. *Id.* § 3710a(c)(7)(B).

commercialized by private companies.[138] The agency's efforts to expand the frontiers of medicine demonstrate more poignantly than any of its initiatives in the past the indispensable role that it plays in the vibrancy of the private health care sector and in creating the future of the pharmaceutical industry. Two of its efforts in this regard are particularly important in nurturing the private market as it helps to transform medical science.

1. The Human Genome Project

The first of NIH's efforts to move medicine toward new horizons is the immense initiative to map the entire set of human genes known as the Human Genome Project (HGP).[139] The molecular structure of the genetic makeup of all living creatures was discovered in 1953 when James Watson and Francis Crick delineated the composition of deoxyribonucleic acid (DNA), the chemical building block of genes.[140] It was a path-breaking discovery that earned the two scientists Nobel Prizes.[141]

a. The quest to map the human genome

Applications of this knowledge were relatively slow to advance for the first decades after its discovery.[142] That began to change in the 1970s, when techniques were developed to manipulate the genetic structure of microorganisms.[143] With them, the era of custom-designed life forms had begun.[144] The door to commercialization of these creations was opened in 1980 with the Supreme Court's ruling in Diamond v. Chakrabarty that artificially created life forms could be patented.[145] With legal protection for its inventions assured, the biotechnology industry was born.

Designer microorganisms found an array of uses, but the real promise of genetic science lay in its applications to human health. Many diseases have been found to have genetic causes, making treatment and prevention

138. *See Licensing & Royalties*, NAT'L INSTS. OF HEALTH, OFFICE OF TECH. TRANSFER, http://www.ott.nih.gov/licensing_royalties/royalties_administration.aspx (last visited Sept. 17, 2012).

139. *About the Human Genome Project*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Sept. 19, 2011), http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml.

140. *The Francis Crick Papers: The Discovery of The Double Helix, 1951-1953*, U.S. NAT'L LIBRARY OF MED., http://profiles.nlm.nih.gov/ps/retrieve/Narrative/SC/p-nid/143 (last visited Sept. 12, 2012).

141. *The Nobel Prize in Physiology or Medicine 1962*, NOBELPRIZE.ORG,http://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/ (last visited Oct. 5, 2012).

142. *See* Julie Ann Miller, *Spliced Genes Get Down to Business*, 117 SCI. NEWS 202, 202 (1980).

143. *Id.*

144. *See id.*

145. Diamond v. Chakrabarty, 447 U.S. 303, 318 (1980).

by conventional means difficult or impossible.[146] By understanding the genetic basis for these conditions, scientists foresaw the possibility of curing or preventing them by manipulating the actual composition of genes.[147] At the least, tests could be devised to determine the extent to which individual patients were susceptible.[148]

During the 1980s, researchers were able to pinpoint the genetic mechanisms behind several devastating conditions and in some cases to develop tests to diagnose them.[149] A major breakthrough along these lines was the creation in 1986 of a test for susceptibility to Huntington's Disease, a devastating brain affliction whose occurrence is determined entirely by genetic factors.[150] However, humans have thousands of genes, and interactions between them can be as important in shaping physiological effects as their individual composition.[151] The full potential of genomic medicine could only be realized if the full set of human genes, known as the human genome, were delineated.

Mapping the entire human genome required a massive effort.[152] However, while the possibilities for improving health were enormous, the specific applications to which it might lead were speculative.[153] This was a prime example of basic research with an indeterminate payoff. Once the map of the genome had been created, it would be a public good that could facilitate research to benefit everyone, but exactly how the map could be

146. *See* Timothy P. O'Connor & Ronald G. Crystal, *Genetic Medicines: Treatment Strategies for Hereditary Disorders*, 7 NATURE REVS. GENETICS 261, 261 (2006).

147. *See id.* at 261-62.

148. *Gene Testing*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Sept. 17, 2010), http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetest.shtml.

149. Kathleen McAuliffe & Sharon McAuliffe, *Keeping up with the Genetic Revolution*, N.Y. TIMES MAG., Nov. 6, 1983, http://www.nytimes.com/1983/11/06/magazine/keeping-up-with-the-genetic-revolution.html?pagewanted=all; *e.g.*, *Learning about Tay-Sachs Disease*, NAT'L HUMAN GENOME RESEARCH INST. (March 17, 2011), http://www.genome.gov/10001220 (The Hex-A gene, whose mutation is the cause of Tay-Sachs disease was isolated in 1985); *e.g.*, *Learning about Cystic Fibrosis*, NAT'L HUMAN GENOME RESEARCH INST. (Sept. 27, 2011), http://www.genome.gov/10001213 (The Cystic Fibrosis Transmembrane Regulator gene, the cause of Cystic Fibrosis, was discovered in 1989).

150. Gwen Terrenoire, *Huntington's Disease and the Ethics of Genetic Prediction*, 18 J. MED. ETHICS 79, 79 (1992).

151. *See* W. Gregory Feero et al., *Genomic Medicine – An Updated Primer*, 362 NEW ENG. J. MED. 2001, 2001, 2002 (2010).

152. *See* Int'l Human Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860, 860 (2001).

153. *See The Human Genome Project & the Private Sector: A Working Partnership*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Nov. 10, 2005), http://www.ornl.gov/sci/techresources/Human_Genome/project/privatesector.shtml.

applied depended on further research on an applied level.[154] As with other basic research, the natural sponsor for such a venture was the government.[155]

Recognizing the potential need, Congress authorized initial funding in 1988 for a joint effort of the federal Department of Energy (DOE) and NIH to map the human genome.[156] In 1990, NIH formally launched the HGP within a new National Center for Human Genome Research, later renamed the National Human Genome Research Institute (NHGRI).[157] DOE's role was to promote research into the effects of radiation on genetic mutations.[158] The HGP relied both on scientists within the government and on researchers at numerous external organizations.[159]

b. The HGP's fruits

The HGP produced a first draft of the genome's map containing 90 percent of its contents in 2001 and a final version in 2002 with the entire set of genes, several years ahead of schedule.[160] The speed was due in part to an implicit, and unexpected, collaboration with the private sector.[161] To pique the interest of private scientists and to help them in joining the effort, the HGP in 1996 began placing all findings in a public database within 24 hours of their disclosure with no limits on their use.[162] In 1998, a private company, Celera Corporation, took up the challenge of using this information by initiating an effort to develop a map of its own.[163] A friendly competition ensued,[164] and it ended with HGP and Celera officials jointly

154. Kathy Hudson, *The Human Genome Protect: A Public Good*, 12 HEALTH MATRIX 367, 373 (2002); *see The Human Genome Project & the Private Sector: A Working Partnership*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Nov. 10, 2005), http://www.ornl.gov/sci/techresources/Human_Genome/project/privatesector.shtml.

155. *See* CONG. BUDGET OFFICE, R&D, *supra* note 43, at 3.

156. Michael Abramowicz, *The Human Genome Project in Retrospect*, 50 ADVANCES IN GENETICS 231, 241-42 (2003).

157. *Id.* at 242.

158. *Id.* at 239 n.47.

159. *Id.* at 242.

160. *History of the Human Genome Project*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (June 4, 2012), http://www.ornl.gov/sci/techresources/Human_Genome/project/hgp.shtml [hereinafter *History of the Human Genome Project*].

161. *See* FIELD, *supra* note 23, at 221.

162. *Id.*

163. *U.S. Human Genome Project Research Goals*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (July 21, 2008), http://www.ornl.gov/sci/techresources/Human_Genome/hg5yp/.

164. *Major Events in the U.S. Human Genome Project and Related* Projects, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Sept. 19, 2008), http://www.ornl.gov/sci/techresources/Human_Genome/project/timeline.shtml [hereinafter *Major Events in the HGP*].

announcing in 2000 that they had completed an initial analysis of the genome's sequence.[165]

The HGP's accomplishment in mapping the entire human genome has been called "one of the remarkable achievements in the history of science."[166] It is a singular accomplishment of government-funded science that promises to revolutionize medical care and with it the entire pharmaceutical industry.[167] In achieving this milestone, NIH laid the foundation for yet another level of pharmaceutical productivity.[168]

Of course, mapping the genome is only the first step in bringing the promise of genomic medicine to fruition. The next step is to devise applications for this new knowledge.[169] This step, as the previous one, relied on input from both the government and the private sector. Starting in 1993, as work on the genome map was proceeding, NIH scientists began investigating the function of various genes as soon as they had been identified along with their roles in human health and disease.[170] Soon thereafter, several private companies began doing the same.[171] Within ten years, several hundred diagnostic tests had been developed, and initial experiments had been launched at actual gene therapy in which new genes are inserted in patients to replace defective ones.[172]

Genomics today is fast becoming a standard part of medical practice in several areas. Its effect is particularly pronounced in the field of oncology.[173] In an especially important advance, scientists discovered in the 1990s that mutations in two genes that were labeled BRCA1 and BRCA2 significantly

165. *Id.*

166. *International Consortium Completes Human Genome Project*, NAT'L HUMAN GENOME RESEARCH INST. (April 14, 2003), http://www.genome.gov/11006929/.

167. *See Potentials Benefits of Human Genome Project Research*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Oct. 9, 2009), http://www.ornl.gov/sci/techresources/Human_Genome/project/benefits [hereinafter U.S. DEP'T OF ENERGY, OFFICE OF SCI., *Potential Benefits*].

168. *See Human Genome Project*, NAT'L INSTS. OF HEALTH (Feb. 14, 2011), http://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=45.

169. *Medicine and the New Genetics*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Sept. 19, 2011), http://www.ornl.gov/sci/techresources/Human_Genome/medicine/medicine.shtml.

170. Francis S. Collins, *Shattuck Lecture, Medical and Social Consequences of the Human Genome Project*, 341 NEW ENG. J. MED. 28, 30-34 (1999) [hereinafter Collins, *Shattuck Lecture*].

171. *E.g.*, Shanshan Zhang, Comment, *Proposing Resolutions to the Insufficient Gene Patent System*, 20 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1139, 1153-54 (2004).

172. Collins, *Shattuck Lecture*, *supra* note 170, at 30-34; *Gene Therapy*, U.S. DEP'T OF ENERGY, OFFICE OF SCI. (Aug. 24, 2011), http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml.

173. *See* C. Lee Ventola, *Pharmacogenomics in Clinical Practice: Reality and Expectations*, 36 PHARMACY & THERAPEUTICS 412, 414 (2011).

increase a woman's chance of developing breast and ovarian cancer.[174] A test for these mutations was devised and is now routinely used by clinicians to advise women of their cancer risk.[175] It is administered by a private company, Myriad Genetics, which holds a patent on the genes involved.[176] Myriad's business of testing for BRCA mutations has proven extremely profitable and has attracted considerable interest from investors.[177]

By the time the HGP had been completed, it had cost the government $3.8 billion, $2.8 billion of which came from the NIH.[178] However, the biggest financial payoff from this investment has been in the private sector. An estimate by the Battelle Memorial Institute put the amount of economic activity generated by the HGP at $67 billion a year, including the steady creation of tens of thousands of jobs.[179] Genomics-related industries now employ about 310,000 workers.[180] Battelle pegged the total amount of economic output driven by the HGP since its inception at $796 billion and the total amount of personal income generated by this output at $244 billion.[181] This financial growth has returned an estimated $49 billion to the government in increased tax revenue, $3.7 billion of which was generated in 2010 alone.[182]

c. The dawn of personalized medicine

As remarkable as the HGP's contribution to the private sector has been, its most significant returns are yet to come. Based on their understanding of the human genome, scientists are learning how to customize drugs to the

174. Robert Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 GENETICS MED. S15, S18 (2010).

175. *BRCA1 and BRCA2: Cancer Risk and Genetic Testing*, NAT'L CANCER INST. (May 29, 2009), http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA.

176. Cook-Deegan et al., *supra* note 174, at S20.

177. Andrew Pollack, *Despite Gene Patent Victory, Myriad Genetics Faces Challenges*, N.Y. TIMES, Aug. 24, 2011, http://www.nytimes.com/2011/08/25/business/despite-gene-patent-victory-myriad-genetics-faces-challenges.html?pagewanted=all.

178. Gautam Naik, *Report Touts Economic Impact of Gene Project*, WALL ST. J., May 11, 2011, http://online.wsj.com/article/SB10001424052748704681904576315253143162630.html.

179. BATTELLE TECH. P'SHIP PRACTICE, ECONOMIC IMPACT OF THE HUMAN GENOME PROJECT 14 (2011), *available at* http://battelle.org/docs/default-document-library/economic_impact_of_the_human_genome_project.pdf?sfvrsn=2.

180. *Id.*

181. *Id.* at 15.

182. *Id.* at ES-2, ES-3; Paul Basken, *Federal Spending on Science Pays Off, Analyses by Research Advocates Say*, CHRONICLE HIGHER EDUC., May 10, 2011, http://chronicle.com/section/About-the-Chronicle/83.

genetic makeup of individual patients.[183] This ability will enable clinicians to avoid using drugs that are destined to be ineffective or to produce significant adverse reactions in some of these who receive them.[184] Many in the pharmaceutical industry see the dawn of an era of personalized medicine in which products can be tailored to each patient's metabolic needs.[185] The clinical potential of this new approach to medication is enormous.

As with much of genomics overall, the initial focus of personalized medicine in pharmaceuticals has been in oncology.[186] Drugs that treat cancer are notorious for the variability of their effectiveness.[187] Chemotherapy agents that achieve miracle remissions in some patients leave others with no improvement.[188] Physicians have long suspected that the genetic makeup of patients, and of their tumors, is crucial to determining how they will respond.[189] With a genetic profile in hand, they can do so. Several targeted drugs have so far been developed for use with companion diagnostic tests, including Herceptin for metastatic breast cancer, Erbitux for metastatic colorectal cancer, and Gleevec for gastrointestinal tumors.[190]

Based on the HGP's map of the genome, new treatments tailored to genetic profiles will continue to emerge.[191] Eventually, they will replace many of the conventional medicines in use today.[192] Their introduction will transform the scientific and economic foundations of the pharmaceutical industry, thanks to a major initiative, the HGP, launched and funded by the government.

183. *Frequently Asked Questions about Genetic and Genomic Science*, NAT'L HUMAN GENOME RESEARCH. INST. (Feb. 27, 2012), http://www.genome.gov/19016904.

184. *Id.*

185. *Id.*

186. *E.g.*, James C. Salwitz, *The Future is Now: Personalized Medicine*, AM. CANCER SOC'Y (April 18, 2012), http://www.cancer.org/Cancer/News/ExpertVoices/post/2012/04/18/The-Future-is-Now-Personalized-Medicine.aspx.

187. Melissa Marino, *More on the Menu: Expanding the Selection of Cancer Therapies*, MOMENTUM, Fall 2009, at16, 18.

188. Leigh MacMillan, *A Perfect Fit: Cancer Medicines get Personal(ized)*, MOMENTUM, Fall 2009, at 8, 10.

189. *Id.* at 11-12.

190. Margaret A. Hamburg & Francis S. Collins, *The Path to Personalized Medicine*, 363 NEW ENG. J. MED. 301, 303 (2010).

191. *See* U.S. DEP'T OF ENERGY, OFFICE OF SCI., *Potential Benefits*, *supra* note 167.

192. *See generally* L.J. Lesko, *Personalized Medicine: Elusive Dream or Imminent Reality?*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 807 (2007) (discussing the shortcomings of traditional medicine and the transition to personalized medicine).

2. National Center for Advancing Translational Sciences

While there have been many success stories, the bridge between basic research and commercial applications can sometimes be difficult to cross. With drugs taking up to a decade and by some estimates more than a billion dollars on average to bring from concept to market and a failure rate of over 95%, pharmaceutical companies often hesitate to commit the needed resources when the end result is uncertain.[193] This reluctance is most often displayed when a drug represents a novel approach to treatment that does not yet have a track record, a category that includes most genomic drugs.[194] As a result, companies have been slower to delve into genetic drug development than many medical experts had initially hoped.[195]

The pipelines of conventional drugs wending their way through the testing and development process began to shrink in the 1990s, and, consequently, the rate of FDA approvals for new drugs based on novel therapeutic approaches also began to decline.[196] Rather than taking the chance of achieving breakthroughs in genomics, many companies took the opposite course of reducing investments in research.[197] At the same time, venture capital firms started to hesitate in providing investment capital to small biotechnology companies for risky forays into genetics.[198] Progress toward realizing the full promise of genetic medicine slowed dramatically as the industry grappled with the confines of its traditional economic model.[199]

For NIH, the hesitation of private industry to commercialize the fruits of government-funded basic research represented a threat to its underlying mission.[200] Historically, the agency has been able to rely on the profit potential of new drugs to motivate industry to move drugs from concepts to

193. Matthew Herper, *The Truly Staggering Cost of Inventing New Drugs*, FORBES, Feb. 10, 2012, http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/. The exact cost is controversial, and some estimates are lower. However, they are still in the range of hundreds of millions of dollars. *See* Christopher P. Adams & Van V. Branter, *Estimating the Cost of New Drug Development: Is it Really $802 million?*, 25 HEALTH AFF. 420, 424 (2006).

194. *See* Hamburg & Collins, *supra* note 190, at 301.

195. *See id.*; *see* Francis S. Collins, *Reengineering Translational Science: The Time is Right*, SCI. TRANSLATIONAL MED., July 6, 2011, at 1, 2 [hereinafter Collins, *Reengineering Translational Science*].

196. Kurt Samson, *New NIH Translational Research Center Plan Moves Forward: What It Could Mean for Neurology*, NEUROLOGY TODAY, April 7, 2011, at 39, 39; *see* Nellie Bristol, *NIH Proposes New Drug Development Centre*, 377 LANCET 705, 705 (2011).

197. Collins, *Reengineering Translational Science*, *supra* note 195, at 2.

198. *See id.*

199. *See* Bristol, *supra* note 196, at 705.

200. *See* Collins, *Reengineering Translational Science*, *supra* note 195, at 4-5.

clinical applications.[201] If companies are unable or unwilling to do so, then the growing array of NIH-funded scientific discoveries will lie fallow.

In the reluctance of private companies to commercialize genomics and personalized medicine, the agency saw the need to move proactively.[202] If industry were not in a position to create its future on its own, the government would have to do it. For several years, NIH considered ways in which it could take the lead in turning genetic discoveries into marketable products. In its view, the gap between basic and clinical research required a new form of investigation that would translate scientific findings into potential applications. This scientific endeavor has come to be called "translational research."[203]

The job of stimulating this new kind of scientific inquiry called for novel approaches. Starting in the early 2000s, NIH began identifying and implementing several of them with the goal of attacking the problem from different angles.[204] The focus of its efforts was on enticing researchers into the new field and providing them with appropriate training.[205] To that end, NIH funded the "Pioneer Award" to support creative problem solving.[206] It also devoted funding to facilities and to training of investigators.[207] It promoted the creation of new resources, like clinical trial networks, biospecimen repositories, and molecular screening libraries.[208] It also considered ways of restructuring itself to better accommodate its emerging translational role.[209] The first step in this process was to launch a new funding program known as "Clinical and Translational Science Awards" to promote the development of academic centers to support translational work.[210]

201. WENDY H. SCHACHT& JOHN R. THOMAS, CONG. RESEARCH SERV., RL 32324, FEDERAL R&D, DRUG DISCOVERY, AND PRICING: INSIGHTS FROM THE NIH-UNIVERSITY-INDUSTRY RELATIONSHIP 23 (2006).

202. Hamburg & Collins, *supra* note 190, at 301; *Translational Research*, NIH COMMON FUND OFFICE OF STRATEGIC COORDINATION, NAT'L INSTS. OF HEALTH (Jan. 1, 2011), http://commonfund.nih.gov/clinicalresearch/overview-translational.aspx.

203. NIH COMMON FUND OFFICE OF STRATEGIC COORDINATION, NAT'L INSTS. OF HEALTH, *supra* note 202.

204. *See* Elias A. Zerhouni, *Translational and Clinical Science – Time for a New Vision*, 353 NEW ENG. J. MED. 1621, 1621 (2005).

205. *Id.*

206. *Id.*

207. *Id.* at 1622.

208. *Id.*

209. *See* Bristol, *supra* note 196, at 705-06.

210. Zerhouni, *supra* note 204, at 1622.

The NIH's bureaucratic reshaping took a dramatic turn in 2010 under the directorship of Dr. Francis Collins, who had led the HGP.[211] He proposed a new center within the agency devoted explicitly to translating genomic and other cutting-edge science into clinical applications. The National Center for Advancing Translational Sciences (NCATS) was conceived that year and implemented in 2011.[212] Its mission is to identify and remedy "bottlenecks" that stand between scientific discovery and clinical applications.[213] In Dr. Collins' view, these arise in large part from the novelty of the paradigm for genetic drug development.[214] Genomics, he believes, has revealed ". . . that the entire framework of medical taxonomy requires rethinking and that therapeutics of the future likely will be designed with cellular networks in mind, rather than being limited by historical designations of disease category."[215]

The biggest bottlenecks lie between the discovery of genes that can cause diseases and the initiation of research to test ways to control them.[216] Without an established drug development road to follow, companies are reluctant to forge ahead on new ones.[217] In a market-based economy, each company looks to its own interests. For many pharmaceutical firms that are peering ahead at a dramatically altered economic landscape, that means limiting exposure to financial risk. The safest course is stand aside and let others test the waters.[218] This leaves the government as the only entity with the mission of protecting larger national interests and the resources to do so.[219]

NCATS focuses its efforts on the initial steps in the drug development process.[220] That is the time when drug testing begins, and the process is least attractive for private investors, because the chances of success are

211. *See generally* Meredith Wadman, *One Year at the Helm*, 466 NATURE 808 (2010) (detailing Collins' first year in office as NIH Director, including a new focus on translational science and a stronger emphasis on genomics).

212. Bristol, *supra* note 196, at 705 (explaining that the center "create[s] a more systematic approach to moving basic discovery research into marketable products" in general; however, in promoting the project Collins specifically noted his disappointment in the advancement of genetic medicines); *Authorization*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS., NAT'L INSTS. OF HEALTH, http://www.ncats.nih.gov/about/budget/authorization.html (last visited Aug. 17, 2012).

213. Collins, *Reengineering Translational Science*, *supra* note 195, at 1.

214. *See id.* at 1-2.

215. *Id.* at 2.

216. *Id.* at 1.

217. *See* Hamburg & Collins, *supra* note 190, at 301.

218. *See* Collins, *Reengineering Translational Science*, *supra* note 195, at 2.

219. *See id.* at 3.

220. *Id.* at 5.

most uncertain and the expected cost is greatest.[221] The new center will carry the ball for new drugs through as much of this phase as necessary until a private company feels comfortable taking over.[222] It will start with preclinical studies both in laboratories and in animals and will follow this with testing in humans if a drug candidate seems promising.[223] If the drug fails, the government will have borne the cost. If it succeeds through this phase, the chance that it will eventually reach the market is greatly enhanced. At that point, the Center will actively seek a private partner.[224]

The new center will not try to actually bring new drugs to market. NIH is not interested in moving into the commercial sphere.[225] The goal is instead to create the conditions that enable the competitive market to work in bringing genomic therapies to patients as it has in producing traditional drugs.[226] As the pillar that has supported private pharmaceutical innovation for the better part of the past century, NIH stands eager to extend that mission into this new terrain. It seems the more scientists learn about the way genes function, the more they find they have to learn to apply discoveries to the needs of patients. That requires a robust private sector to commercialize new products.[227] However, the investment in basic knowledge that is required is still too great to entice most pharmaceutical firms to make the leap.[228] The scientific infrastructure does not yet exist to translate the new paradigm of biomedical research into a market-based business.[229] Industry needs the government to create it, and, as it has in so many other ways, NIH has taken up the challenge.

IV. GOVERNMENT SUPPORT FOR THE PHARMACEUTICAL INDUSTRY BEYOND NIH

While the role of NIH is invaluable in generating the essential intellectual fuel on which the pharmaceutical research engine runs, it is far

221. *Re-engineering Translational Sciences*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS., NAT'L INSTS. OF HEALTH, http://www.ncats.nih.gov/research/reengineering/reengineering.html (last visited Aug. 17, 2012) [hereinafter NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS., *Re-engineering Translational Sciences*].

222. *See* Samson, *supra* note 196, at 42.

223. Collins, *Reengineering Translational Science*, *supra* note 195, at 2; NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS., *Re-engineering Translational Sciences*, *supra* note 221.

224. *See* Bristol, *supra* note 196, at 705.

225. John C. Reed, *NCATS Could Mitigate Pharma Valley of Death*, GENETIC ENG'G & BIOTECHNOLOGY NEWS, May 15, 2011, http://www.genengnews.com/gen-articles/ncats-could-mitigate-pharma-valley-of-death/3662/.

226. *Id.*

227. Collins, *Reengineering Translational Science*, *supra* note 195, at 5.

228. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 29.

229. *See* ORG. FOR ECON. CO-OPERATION AND DEV., BIOMEDICINE AND HEALTH INNOVATION, SYNTHESIS REPORT 8 (2010), *available at* http://www.oecd.org/science/biotechnologypolicies/46925602.pdf.

from being the only major government program that supports and maintains the industry. Drug companies depend on a range of other public initiatives, both directly and indirectly, for much of their economic viability. A few of them illustrate the extensiveness of that reliance.

A. The Largest Customer for Pharmaceuticals

Prescription drugs are sold in the United States largely through a private market, but it is one that has come to rely almost entirely on third-party payment by insurance plans. In 1960, insurance covered 4% of prescription drug spending in the United States.[230] In 2008, that portion was almost 80%.[231] The most dramatic change occurred during the 1990s, when the share increased from 44.5 to 72.3%.[232] As the rate of coverage has grown, the fraction of insurance represented by private and by public sources has remained about the same.[233]

In 2008, government programs picked up the tab for $87 billion of the $234 billion that Americans spent on outpatient prescription drugs.[234] The two largest contributors are Medicare at over $55 billion and Medicaid at over $25 billion.[235] In addition to drugs taken on an outpatient basis, these programs also pay billions of dollars a year for drugs administered in physicians' offices and to hospital inpatients.[236]

Medicare first covered outpatient prescription drugs in 2006, when Part D of the program was launched.[237] In 2010, this benefit represented 13.4% of the program's overall budget.[238] Medicare covers prescription drugs

230. *See* NAT'L CTR. FOR HEALTH STATISTICS, CTR. FOR DISEASE CONTROL & PREVENTION, DHHS PUB. NO. 2011-1232, HEALTH, UNITED STATES, 2010, at 372 (2011).

231. *See id.*

232. *See id.*

233. *See id.*

234. *See id.*

235. JOHN HOLAHAN ET AL., KAISER FAMILY FOUND., MEDICAID SPENDING GROWTH OVER THE LAST DECADE AND THE GREAT RECESSION, 2000-2009, at 8 (2011), *available at* www.kff.org/medicaid/upload/8152.pdf; *see* NAT'L CTR. FOR HEALTH STATISTICS, *supra* note 230, at 372; *see* KAISER FAMILY FOUND., MEDICARE SPENDING, *supra* note 16, at 1.

236. MEDICARE PAYMENT ADVISORY COMM'N, *supra* note 16, at 169; Linda Elam, *Prescription Drugs Under Medicaid in* HANDBOOK OF PHARMACEUTICAL PUBLIC POLICY 87, 94 (Thomas R. Fulda & Albert I. Wertheimer eds., 2007); *see* KATHERINE YOUNG ET AL.,KAISER FAMILY FOUND., MEDICAID'S ROLE FOR DUAL ELIGIBLE BENEFICIARIES 13 (2012), *available at* http://www.kff.org/medicaid/upload/7846-03.pdf (see acute care services, of which $1.524 billion are inpatient services and $810 million are prescribed drugs); *see, e.g.*, OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUMAN SERVS., OEI-03-02-00660,MEDICAID REBATES FOR PHYSICIAN-ADMINISTERED DRUGS 1, 15-16 (2004).

237. *See* Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (codified at 42 U.S.C. § 1395 (2012)).

238. DEP'T OF HEALTH & HUMAN SERVS., FISCAL YEAR 2010 BUDGET IN BRIEF 53 (2009).

administered in a physician's office through Part B and has done so since the program's inception in 1966.[239] Additional drug spending comes under Part A through payments to hospitals for inpatient care and through several other aspects of the program's coverage, including reimbursement for nursing care and for hospital outpatient services.[240]

Medicaid has covered outpatient prescription drugs in most states since its launch in 1966.[241] In 2008, this expenditure represented about 7% of the program's budget nationally.[242] In many states, it also represents the fastest growing category of spending.[243]

Some patients need thousands of dollars a year in prescription drugs.[244] A course of treatment with some oncology medications can cost over $100,000 a year.[245] These customers would be locked out of the market for these lifesaving products were coverage by a third-party payer not available.[246] By providing the financial means to help patients purchase drugs, insurance also increases the size of the potential market for pharmaceutical companies and the amounts they can charge for their products.[247]

Not surprisingly, growth in insurance coverage for prescription drugs has tracked growth in overall national drug spending. During the 1990s, when the rate of coverage almost doubled, overall prescription expenditures also experienced their highest level of growth, almost tripling from $40.3 billion to $120.6 billion.[248] The trend continued during the early 2000s, when Medicare prescription spending rose from $2 billion in 2000 to over $39

239. Scherer, *supra* note 24, at 930; *FAQs – Frequently Asked Questions*, U.S. SOCIAL SEC. ADMIN. (May 15, 2012), http://www.ssa.gov/history/hfaq.html.

240. DEP'T OF HEALTH & HUMAN SERVS., *supra* note 238, at 53.

241. John D. Klemm, *Medicaid Spending: A Brief History*, HEALTH CARE FINANCING REV., Fall 2000, at 105, 106; *see* BRIAN K. BRUEN, KAISER FAMILY FOUND.,STATES STRIVE TO LIMIT MEDICAID EXPENDITURES FOR PRESCRIBED DRUGS 8 (2002), *available at* http://www.kff.org/medicaid/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=14111.

242. HOLAHAN ET AL., *supra* note 235, at 8.

243. *See* BRUEN, *supra* note 241, at 1.

244. Walid F. Gellad et al., *The Financial Burden From Prescription Drugs Has Declined Recently for the Nonelderly, Although it is Still High for Many*, 31 HEALTH AFF. 408, 410-11 (2012).

245. *The Costly War on Cancer*, ECONOMIST, May 26, 2011, http://www.economist.com/node/18743951.

246. *See e.g.*, *id.*; *see* KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS, *supra* note 29, at 5.

247. CONG. BUDGET OFFICE, R&D, *supra* note 43, at 4, 43; David H. Kreling, *The Market for Pharmaceuticals: The Big Picture*, *in* HANDBOOK OF PHARMACEUTICAL PUBLIC POLICY 43, 62 (Thomas R. Fulda & Albert I. Wertheimer eds., 2007).

248. NAT'L CTR. FOR HEALTH STATISTICS, *supra* note 230, at 372.

billion in 2006 with the launch of Part D.[249] During these six years, national drug expenditures almost doubled, from $120.6 billion to $217 billion.[250]

The pharmaceutical industry was robust and profitable long before Medicare and Medicaid began covering its products.[251] It would undoubtedly still have been a major economic presence even without them.[252] It is also possible that some patients who rely on these programs might have been able to find alternative insurance in the private market or to pay more of the cost out of their own pockets.[253] However, it is unlikely that Americans would have been able to come up with $87 billion a year for prescriptions on their own.[254] Beyond funding the creation of new drugs through NIH, the government has positioned itself as the most important consumer in the private market through which drugs are sold.[255]

B. Quality Assurance Through the FDA

It is difficult to sell a product if the public has no confidence in it. This is all the more true if the product can cause serious injury or death. That is the position the pharmaceutical industry is in when it sells medicines that can achieve miraculous benefits in some cases but that under some circumstances can produce serious harm.

Americans, by and large, trust the safety of the drugs their doctors prescribe.[256] There have certainly been instances in which hazardous products have reached the market, but most of the time, a vast apparatus of quality oversight keeps that from happening.[257] The public reassurance that this engenders is crucial to sustaining the industry. If patients worried about experiencing severe harm every time they filled a prescription, many would balk at filling them and many doctors at writing them.

1. The Growth of FDA Authority Through Scandals

The source of public trust on which the pharmaceutical market relies was almost entirely created and is almost entirely maintained by the

249. *See id.*

250. *Id.*

251. *See* RACHEL CHRISTENSEN SETHI, EMP. BENEFIT RESEARCH INST., ISSUE BRIEF NO. 265, PRESCRIPTION DRUGS: RECENT TRENDS IN UTILIZATION, EXPENDITURES, AND COVERAGE 4 (2004), *available at* http://www.ebri.org/pdf/briefspdf/0104ib.pdf.

252. *See id.* at 5.

253. *See id.* at 1, 13-14.

254. In 2008, the government's outpatient prescription drug expenditures totaled $87 billion dollars.*See* NAT'L CTR. FOR HEALTH STATISTICS, *supra* note 230, at 372.

255. *See* KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS, *supra* note 29, at 7; *see* CHRISTENSEN SETHI, *supra* note 251, at 11, 13.

256. *See* FIELD, *supra* note 23, at 139.

257. *See id.* at 138-39.

government. It begins with oversight of the professions most directly involved in bringing drugs to patients.[258] Physicians who decide what drugs a patient should take do so under licenses granted by the state in which they practice.[259] Pharmacists who dispense the prescriptions are also licensed by their state.[260] Licensure provides for a review of basic qualifications before these professionals begin practice and for ongoing supervision of their quality once they do.[261]

However, the greatest source of reassurance for patients is in the quality of the drugs themselves, and that is provided by the FDA.[262] The agency came into being in 1906, a time when pharmaceutical manufacturing could hardly be called an industry.[263] Drugs were as likely to be sold by a physician or compounded by a pharmacist as to be centrally manufactured.[264] The range of available drugs and their capabilities were extremely limited.[265] Most of the products that are commonly used today, including almost all antibiotics, had yet to be invented.[266] The law that created the FDA, the Pure Food and Drug Act, was passed after scandals involving two popular cold remedies were described in the popular press.[267] Those revelations, along with publication in 1906 of *The Jungle* by Upton Sinclair, which exposed dangerous and unsanitary conditions in the meatpacking industry, had undermined public confidence in the food and drug supply.[268]

Congress expanded the FDA's authority and created the basic regulatory structure that oversees the nation's drug supply today about 30 years later

258. ROBERT D. MILLER & REBECCA C. HUTTON, PROBLEMS IN HEALTH CARE LAW 77 (8th ed. 2000).

259. *Id.* at 78.

260. *Id.*

261. *Id.* at 77-78.

262. 2004 polling data indicate that 70% of Americans have a great deal or a moderate amount of confidence in the FDA to ensure prescription drug safety, although 37% said their confidence had diminished in the previous few years. Julie Appleby, *Poll: Confidence in FDA Still Strong Despite Blunders*, USA TODAY, Nov. 24, 2004, at 2A.

263. Robert I. Field, *A Taxonomy of American Health Care Regulation: Implications for Health Reform*, 17 TEMP. POL. & CIV. RTS. L. REV. 605, 608-09 (2008).

264. *See generally* PAUL STARR, THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE 127-134 (1982) (detailing the push to legitimize the drug industry).

265. *See* Wallace F. Janssen, *About FDA: The Story of the Laws Behind the Labels*, U.S. FOOD & DRUG ADMIN. (June 1981), http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm.

266. Jon Clardy et al., *The Natural History of Antibiotics*, 19 CURRENT BIOLOGY R437, R437 (2009).

267. Janssen, *supra* note 265.

268. UPTON SINCLAIR, THE JUNGLE (1906); *see also* PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION 28 (2003).

after another major scandal revealed a serious flaw in the 1906 scheme.[269] The old law had given the FDA authority to pull drugs from the market if they were found to be dangerous, and to prevent further sale of them.[270] It also permitted the agency to block manufacturers from making false claims about the composition of their products.[271] However, before the FDA could act, the product and the claims about it had to have already reached the public.[272]

In 1937, a dangerous antibiotic preparation entered the market without sufficient testing of its safety.[273] Elixir of sulfanilamide contained a mixture of an antibiotic and a sweet-tasting solvent that made it appealing to children.[274] The solvent turned out to be highly toxic, with a chemical structure that was similar to antifreeze.[275] By December of that year, it had caused 107 deaths in 15 states, mostly of children.[276] The FDA banned the manufacturer from selling any more of it, but was only empowered under existing law to act after the harm had already been done.[277]

Congress tightened the restrictions on drug marketing in 1938 to require that the FDA review the safety of new drugs before they could reach patients.[278] Under new authority granted to it by the Food, Drug, and Cosmetic Act, the agency implemented a regulatory scheme under which new drugs must undergo years of testing before they may be sold.[279] The process starts with pre-clinical studies of drug effects in animals and continues with three phases of clinical trials.[280]

These studies can take eight years or more to complete.[281] All of the results must be submitted to the FDA for review before a drug can be

269. Cynthia Crossen, *How Elixir Deaths Led U.S. to Require Proof of New Drugs' Safety*, WALL STREET JOURNAL, Oct. 3, 2005, at B1.

270. *See* Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768.

271. *Id.*

272. *See id.*

273. Crossen, *supra* note 269.

274. *Id.*; *see also* Carol Ballentine, *Taste of Raspberries, Taste of Death The 1937 Elixir Sulfanilamide Incident*, U.S. FOOD & DRUG ADMIN. (1981), http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm.

275. Ballentine, *supra* note 274.

276. *Id.*; *see also* Arthur Hull Hayes, *Food and Drug Regulation After 75 Years*, 11 JAMA 1223, 1223-26 (1981); *see also* HILTS, *supra* note 268, at 92.

277. *See* Ballentine, *supra* note 274.

278. *See* Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938) (codified as amended at 21 U.S.C. § 355 (2006)).

279. *Id.*

280. MARK P. MATHIEU, NEW DRUG DEVELOPMENT: A REGULATORY OVERVIEW 1-14 (1994).

281. *New Drug Development Still Takes Eight Years Despite Faster FDA Review, According to the Tufts Center for the Study of Drug Development*, TUFTS CTR. FOR THE STUDY OF DRUG DEV. (Jan. 2009), http://csdd.tufts.edu/files/uploads/01_-_jan_6,_2009_-_outlook.pdf.

approved.[282] When manufacturing of the drug begins, the agency inspects the plants where it will be made for compliance with standards for safety and cleanliness.[283] It also monitors ongoing use of the drug for signs of adverse effects.[284]

This new regulatory arrangement averted a public health catastrophe about 20 years later. FDA approval was sought for a new drug known as thalidomide that was thought to be helpful when taken by pregnant women in preventing miscarriages and that also worked as a sleeping pill.[285] It had already been approved and was widely prescribed in Europe.[286] However, as use of it spread, so did reports of severe birth defects in the children of women who had taken it. By 1962, there had been more than 5,000 such reports worldwide.[287] In response, the FDA slowed its review process to allow more time for information to accumulate.[288] The link between thalidomide and birth defects eventually became clear and was widely reported in the press.[289] Before the agency had made a final determination, the application for approval was withdrawn.[290]

Had the 1938 law not been in effect at the time, the FDA would have lacked authority to keep thalidomide off the market while it considered the news from Europe of devastating adverse effects. There is no way to know how many tragic birth defects would have occurred in the United States before the agency could have gathered enough evidence to pull it from the market, but it is likely that the number would have been considerable.[291] In response to this near miss, Congress strengthened the FDA's authority yet again in 1962, this time to require that manufacturers establish a drug's efficacy in addition to its safety before the FDA can permit patients to receive it.[292]

Additional refinements and enhancements of the FDA's authority have been enacted over the years.[293] However, prior review of safety and efficacy

282. MATHIEU, *supra* note 280, at 10-11.

283. 21 U.S.C. § 355(d) (2006).

284. 21 C.F.R. § 314.80 (2011).

285. TRENT D. STEPHENS & ROCK BRYNNER, DARK REMEDY: THE IMPACT OF THALIDOMIDE AND ITS REVIVAL AS A VITAL MEDICINE 40-55 (2001).

286. *See* Katherine A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 126 (2007).

287. STEPHENS & BRYNNER, *supra* note 285, at 62-63.

288. Janssen, *supra* note 265.

289. STEPHENS & BRYNNER, *supra* note 285, at 79-99.

290. *Id.* at 54.

291. Janssen, *supra* note 265.

292. *See* FIELD, *supra* note 23, at 123.

293. *Id.* at 124.

remain the primary bases on which it approves new drugs.[294] Drug companies maintain a massive pre-market testing apparatus to generate data to meet the agency's demands in these regards.[295]

2. The FDA Today

The FDA regulatory apparatus as it exists today is far from perfect. A number of drugs have been pulled from the market or subjected to heightened warnings years after approval when new safety hazards came to light.[296] However, incidents of drugs entering the market with unknown and devastating side effects are rare.[297] Countless drug candidates have been blocked before reaching the public because of safety concerns that arise during the years of premarket clinical testing.[298] At the least, the public knows that a tremendous amount of attention has been directed toward the safety of the drugs that are prescribed.[299] Application of consistent regulatory standards also adds stability to the market by reassuring private companies and investors that products will be judged through an established scientific process.[300]

The FDA today is one of the most trusted agencies of the federal government. In a 2004 poll, 70% of the respondents reported having either a great deal or at least a moderate amount of confidence in it.[301] The industry often complains about bureaucratic delays and inefficiency in the drug approval process, but if patients believed that no one was watching over their medications, their willingness to buy the industry's products would be severely compromised.[302] The private pharmaceutical market rests on such a stamp of approval that only an outside impartial force like the government can provide.

294. *See A History of the FDA and Drug Regulation in the United States*, U.S. FOOD & DRUG ADMIN. (2006), http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm093550.pdf.

295. *See* FIELD, *supra* note 23, at 118-20.

296. Janssen, *supra* note 265.

297. *Frequently Asked Questions*, PHARM. RESEARCH & MFRS. OF AM., http://www.phrma.org/about/faq (last visited Sept. 8, 2012).

298. *See* FIELD, *supra* note 23, at 119.

299. *Id.* at 139.

300. Joshua M. Sharfstein, *The FDA – A Misunderstood Agency*, 306 JAMA 1250, 1250 (2011).

301. Appleby, *supra* note 262; *see also* David W. Moore, *Vioxx Recall Hits a Low-Rated Industry*, GALLUP NEWS SERV. (Dec. 1, 2004), http://www.gallup.com/poll/14212/Vioxx-Recall-Hits-LowRated-Industry.aspx.

302. *See* FIELD, *supra* note 23, at 139; Gieringer, *supra* note 23, at 177-78.

C. *Direct Government Market Support*

The government through the FDA also acts affirmatively to shape the private market for pharmaceuticals by developing and sustaining key sectors that might not otherwise exist. These efforts guide the market in directions it would not have taken on its own. A few of them are particularly influential.

1. Facilitating Generics to Create Market Competition

Most importantly, the government has fashioned the competitive dynamics of the overall pharmaceutical market by facilitating the entry of generic drugs. These are products that include the same active ingredient as an existing drug, and they may be sold once the patent on that ingredient has expired.[303] Generic copies usually sell at much lower prices than the original drug and thereby bring an important element of competition to the market that can help to control costs.[304]

The Hatch-Waxman Act speeds the regulatory approval of generics by permitting their manufacturers to piggyback on the results of clinical trials for the original patented product.[305] Rather than repeating all phases of testing, they only have to show that their version is comparable to the original in the amount that the body absorbs.[306] This means that testing can be completed more quickly and cheaply than it would if a full set of trials for safety and efficacy were required.[307] To speed the process further, testing of a generic copy can begin while the original drug's patent is still in force.[308] With this head start, the generic company can have its product approved and ready to be sold as soon as the patent expires.[309]

The Hatch-Waxman Act has dramatically reshaped the market for generic drugs. In 1984, the year it was passed, generics represented just 18.6% of American pharmaceutical sales.[310] By 1997, that share had grown

303. Popular Prescription Drugs Hitting the Market in Generic Form, U.S. FOOD & DRUG ADMIN. (March 15, 2012), http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm296039.htm.

304. *See* C. Scott Hemphill & Mark A. Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, 77 ANTITRUST L.J. 947, 951-52 (2011).

305. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1585 (codified as amended at 21 U.S.C. 355 (2006)).

306. *Id.*

307. *See* Helm, *supra* note 286, at 144.

308. *Id.*

309. *See id.* at 144, 146.

310. WILLIAM ORZECHOWSKI & ROBERT C. WALKER, NAT'L TAXPAYERS UNION FOUND., POLICY PAPER NO. 125, DOSE OF REALITY, HOW DRUG PRICE CONTROLS WOULD HURT AMERICANS 8 (2000).

to 44.3%.[311] Today, most prescriptions filled in the United States are for generics.[312] The ripples of this turnaround have changed the landscape for brand name drugs, as well. With the threat of vigorous generic competition looming once a patent expires, they can no longer rely on a stock of established products to generate profits indefinitely but must continuously fill their pipelines with new drugs that have fresh patent clocks. This is a competitive force the market would lack were it not for this form of active government intervention.

2. Creating a Market for Orphan Drugs

Congress authorized the FDA in 1983 to aid drug companies in producing medications for rare diseases when it passed the Orphan Drug Act.[313] Ailments that are extremely rare are known as "orphan diseases", because the small number of patients who suffer from them leaves potential treatments with a small potential market that is insufficient to generate profits.[314] They include numerous conditions that are debilitating and even life threatening, such as Huntington's Disease, myoclonus, Lou Gehrig's disease, Tourette's syndrome, and muscular dystrophy.[315]

The Act authorized grants, tax credits, and seven years of additional market exclusivity beyond a patent's expiration for drugs that are designed to treat conditions afflicting fewer than 200,000 people.[316] The FDA also gives these products special consideration in the approval process.[317] With this government boost, more than 300 treatments for orphan diseases received FDA approval in the 25 years following the law's enactment, compared with only ten during the previous ten years.[318]

3. Creating a Market for Pediatric Pharmaceuticals

Another significant gap in the private pharmaceutical market has been the attention paid by major companies to the needs of children. Clinical

311. *Id.*

312. *Facts About Generic Drugs*, U.S. FOOD & DRUG ADMIN. (Sept. 19, 2012), http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm.

313. Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended in scattered sections of 15, 21, 26, 35 and 42 U.S.C. (2006)).

314. *Id.* § 1(a).

315. *Id.*

316. *Id.* §§ 2, 4, 5; 21 C.F.R. §§ 316.20(b)(8)(i), 316.21(b) (2012).

317. Orphan Drug Act, § 2.

318. U.S. FOOD & DRUG ADMIN., DEVELOPING ORPHAN PRODUCTS: FDA AND RARE DISEASE DAY 1-2 (2009), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm107301.pdf.

testing for pediatric drugs can be difficult and risky.[319] Children often react differently than adults to medications, and adverse effects can be more severe.[320] To avoid the risks, most clinical trials include only adults as subjects.[321] As a result, the safety and efficacy of new drugs when used to treat children are rarely known with accuracy when they are first approved.[322]

Pediatric testing often does not make financial sense for private companies because of the relatively small portion of the market involved, but there is still a significant need to determine how children will react to new drugs.[323] To remedy this gap in market incentives, Congress in 1997 authorized special incentives to encourage companies to conduct clinical trials in children in the form of FDAMA.[324] That law offered companies a reward of six months of additional market exclusivity after a patent expires for drugs that have undergone pediatric testing.[325] In 1999, the FDA issued a related regulation known as the Pediatric Rule, under which it requires companies to test some new drugs in children.[326] The Act and the regulation are together credited with inducing companies to conduct a substantial number of pediatric studies, thereby expanding the clinical uses as well as the market for many pharmaceutical products.[327]

4. The FDA and the Future of Genomic Medicine

FDA's role in promoting generic drugs, orphan drugs, and pediatric testing of new drugs arose from directives of Congress. In 2010, without waiting for new legislation, the agency acted on its own initiative to reshape the private market in another important area. It took steps to prod pharmaceutical companies to respond to the challenge of commercializing genomic medicine. It did so in partnership with NIH as part of an effort to facilitate the advance of translational science.[328] Under this arrangement,

319. *See Drug Research and Children*, U.S. FOOD & DRUG ADMIN. (Aug. 24, 2011), http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm [hereinafter U.S. FOOD & DRUG ADMIN., *Drug Research and Children*].

320. R. Priyadharsini et al., *A Study of Adverse Drug Reactions in Pediatric Patients*, 2 J. PHARMACOLOGY & PHARMACOTHERAPEUTICS 277, 277 (2011).

321. *Id.*

322. U.S. FOOD & DRUG ADMIN., *Drug Research and Children*, *supra* note 319.

323. *Id.*

324. Food and Drug Administration Modernization Act (FDAMA) of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305 (codified as amended at 21 U.S.C. 355a (2006)).

325. *Id.*

326. 21 C.F.R. § 314.55 (2012).

327. Robert Steinbrook, *Testing Medications in Children*, 347 NEW ENG. J. MED. 1462, 1465-66 (2002).

328. Hamburg & Collins, *supra* note 190, at 301, 304.

NIH promotes research and training, while FDA encourages companies to integrate genomics into their drug development processes.[329] To that end, it tries to coordinate the review of genetic diagnostic tests that predict responsiveness to drugs with review of the drugs themselves.[330] The goal is to facilitate the development of diagnostic-therapeutic combination approaches that aid clinicians, along with a review process that reassures companies that new technologies in which they invest will receive prompt review.[331]

The NIH-FDA partnership builds on NIH's translational medicine initiative that extends the government infrastructure on which the nascent market for genomic medicine rests.[332] In doing so, it will help to promote an even larger and more robust private pharmaceutical industry. The agencies acted in the belief that the market will not grow on its own but rather requires assistance from its indispensable partner, the government. In a joint statement, the heads of the agencies described the model they created as a logical extension of the paradigm on which so much of American industry is built:

> When the federal government created the national highway system, it did not tell people where to drive — it built the roads and set the standards for safety. Those investments supported a revolution in transportation, commerce, and personal mobility. We are now building a national highway system for personalized medicine, with substantial investments in infrastructure and standards.[333]

D. More Government Subsidies Through Tax Breaks

In addition to these forms of regulatory support and funding for the infrastructure on which their research apparatus rests, the government also lends drug companies assistance of a more direct kind. It gives them money in the form of tax credits.[334] This financial boost lets pharmaceutical firms lower their tax bills, and thereby keep more of their income, by devoting resources to research.[335] While the nature of the credits has changed over

329. *See id*. at 302-03.

330. *Id.* at 303.

331. *Id*.

332. *Id.* at 301-02; NAT'L INSTS. OF HEALTH SCIENTIFIC MGMT. REVIEW BD., REPORT ON TRANSLATIONAL MEDICINE AND THERAPEUTICS 4 (2010), *available at* http://smrb.od.nih.gov/documents/reports/TMAT_122010.pdf.

333. Hamburg & Collins, *supra* note 190, at 304.

334. Kenneth C. Whang, *The Applicability of Tax Credits to Medical Research and Development*, AM. ASS'N FOR THE ADVANCEMENT OF SCI. (1999), http://www.aaas.org/spp/cstc/pne/pubs/fundscience/papers/whang.htm.

335. *Id*.

time with amendments to the federal tax code, the underlying mechanism of paying private companies to conduct research has remained.[336]

Three kinds of tax credit are available to companies. A research and experimentation credit allows companies to lower their taxes in return for increasing the amount they spend on in-house research.[337] A basic research credit encourages companies to fund scientific investigations at universities.[338] An orphan drug credit rewards the development of drugs for rare diseases as part of the Orphan Drug Act.[339]

These inducements, worth more than $5 billion a year, do not significantly alter the nature of the industry, and the benefits tend to accrue mainly to larger companies.[340] However, they help to encourage the overall growth of the private research enterprise.[341] In doing so, they form yet another government platform that has helped the private market to flourish.

E. The Most Fundamental Government Support of All: Patents

Beneath the billions of dollars and intricate web of laws and regulations that comprise the government's active intervention to create and sustain the private pharmaceutical market lies an even more fundamental pillar. That is the protection that patent laws confer on its products. Without these laws, the industry could not exist in anything close to its present form.

Patents grant inventors 20 years from the date of filing to prevent anyone else from manufacturing, distributing, or selling their inventions.[342] In effect, inventors enjoy a monopoly during this time and can take advantage of the lack of competition to set prices above those that a free market would sustain.[343] The actual amount of time during which drugs can be marketed exclusively under a patent is less than the full 20 years in practice, because clinical testing and FDA review can eat up as much as half of the full patent term.[344] However, the time remaining once marketing has begun has been more than sufficient to support ample profits for most

336. *See id.*

337. *Id.*

338. *Id.*

339. Whang, *supra* note 334.

340. LAURA TYSON & GREG LINDEN, CTR. FOR AM. PROGRESS, THE CORPORATE R&D TAX CREDIT AND U.S. INNOVATION AND COMPETITIVENESS 2, 35, 45-48 (2012).

341. Whang, *supra* note 334.

342. 35 U.S.C. § 154(a) (2006).

343. *See* Peter Temin, *Technology, Regulation, and Market Structure in the Modern Pharmaceutical Industry*, 10 BELL J. ECON. 429, 443 (1979).

344. Harold M. Silverman, *Overview of Generic Drugs and Drug Naming*, THE MERCK MANUAL HOME HEALTH HANDBOOK (April 2007), http://www.merckmanuals.com/home/print/drugs/trade-name_and_generic_drugs/overview_of_generic_drugs_and_drug_naming.html.

products.[345] Moreover, the exclusive sales period is often extended by other laws, such as the Hatch-Waxman Act and FDAMA.[346]

The exclusive marketing protection granted by patents is vital to the pharmaceutical industry. Companies rely on patent protection as the bedrock of their economic model.[347] Monopoly prices allow them to recoup research and development costs for new products, amass funds to investigate novel therapies that may not make it to market, and generate substantial financial returns.[348] These prices provide the economic underpinning for the emergence of blockbuster drugs that bring companies billions of dollars in sales each year.[349]

The law of patents is rooted in the United States Constitution, which authorizes Congress to protect property rights in inventions.[350] The patent system that Congress established to effectuate this constitutional directive is administered by the USPTO, which decides whether inventions meet the criteria for patentability.[351] Patents were not included in the Constitution or implemented by Congress with the pharmaceutical industry specifically in mind.[352] Rather, they form a key underpinning of our entire economic system.[353] Nevertheless, their application to drugs forms an indispensable part of the infrastructure that supports private pharmaceutical companies. Without this government foundation, the industry would take on a very different, and almost surely less profitable, form.

V. GOVERNMENT SUPPORT IN ACTION: CASE STUDIES OF MEDICAL MIRACLES

Whether they realize it or not, everyone who has taken a prescription drug in the past 50 years has experienced the effects of public-private collaborations first hand. It would be difficult to identify a medication developed during that time that did not emerge from a base of at least

345. ROBIN J. STRONGIN, NAT'L HEALTH POLICY FORUM, HATCH-WAXMAN, GENERICS, AND PATENTS: BALANCING PRESCRIPTION DRUG INNOVATION, COMPETITION, AND AFFORDABILITY 6 (2002).

346. *Id.* at 12, 16.

347. *See* Matthew Herper, *Solving the Drug Patent Problem*, FORBES, May 2, 2002, http://www.forbes.com/2002/05/02/0502patents.html.

348. John H. Barton & Ezekiel J. Emanuel, *The Patents-Based Pharmaceutical Development Process: Rationale, Problems, and Potential Reforms*, 294 JAMA 2075, 2076 (2005).

349. Thompson, *supra* note 110, at 1671; *see, e.g.*, Max Nisen, *The 10 Best Selling Prescription Drugs in the United States*, BUSINESS INSIDER (June 28, 2012), http://www.businessinsider.com/10-best-selling-blockbuster-drugs-2012-6?op=1 ("The top 20 drugs in the United States accounted for $319.9 billion in sales in 2011").

350. U.S. CONST. art. I, § 8, cl. 8.

351. 35 U.S.C. § 153 (2006).

352. U.S. CONST. art. I, § 8, cl. 8; SCHACHT & THOMAS, *supra* note 201, at 2-5.

353. *See* ECON. & STATISTICS ADMIN. & U.S. PATENT & TRADE OFFICE, INTELLECTUAL PROPERTY AND THE U.S. ECONOMY: INDUSTRIES IN FOCUS i-ii, 1-2 (2012).

some government-funded research. Medications for high blood pressure, high cholesterol, cancer, depression, and Parkinson's disease, to name just a few examples, grew out of government-funded research findings.[354] Along with the success of these drugs have ridden the financial fortunes of many major pharmaceutical firms.

Prime examples of successful public-private drug development sit inside the medicine cabinets of millions of Americans. Two of them illustrate especially poignantly the importance of the partnership between NIH-funded discoveries and industry commercialization. One reflects an ad hoc relationship, in which a collaboration evolved over time. The other emerged from an explicit effort by NIH to identify and work with a corporate ally.

A. The Traditional Model: The Story of Statins

Some drug success stories start without a clear plan. A discovery in basic research leads a private firm to devise a potential application that it investigates in its laboratories.[355] Others are more haphazard. A firm may screen thousands of compounds hoping that one of them shows commercial promise based on directions identified in prior research.[356] Whatever the approach, in conventional drug development, private industry takes the laboring oar in vetting drug candidates, after government-funded basic research has pointed it in promising directions.[357] The development of one of the most widely prescribed classes of drugs — statins — vividly tells the tale.

A complex public-private partnership that evolved over the course of several decades led to the development of statins, which today are among the most important pharmacological therapies in medical practice.[358] These drugs are used by millions of people worldwide to reduce blood cholesterol levels.[359] They have proven extremely effective at preventing heart attacks, strokes and other heart-related ailments among those with high cholesterol or other risk factors such as diabetes.[360] Heart disease is the most common

354. NAT'L INSTS. OF HEALTH, PUB. NO. 11-7634, NIH . . . TURNING DISCOVERY INTO HEALTH 2-3, 6-7 (2011), *available at* http://www.nih.gov/about/discovery/viewbook_2011.pdf.

355. Andrew A. Toole, *The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry*, 41 RES. POL'Y 1, 2-3 (2012).

356. Zycher et al., *supra* note 3, at 102, 107, 113.

357. *See* JOINT ECON. COMM., 106TH CONG., BENEFITS OF MEDICAL RESEARCH AND THE ROLE OF THE NIH 9-10 (Chairman, Connie Mack, 2000).

358. Zycher et al., *supra* note 3, at 106 tbl.2, 108.

359. Melinda Wenner Moyer, *The Search Beyond Statins*, 16 NATURE MED. 150, 150 (2010).

360. CONSUMER REPORTS BEST BUY DRUGS, EVALUATING STATIN DRUGS TO TREAT: HIGH CHOLESTEROL AND HEART DISEASE, COMPARING EFFECTIVENESS, SAFETY, AND PRICE 4 (2012), *available at* http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/StatinsUp

cause of death in the United States and around the world, and much of it is caused by the build-up of plaque composed of cholesterol in the arteries.[361] In preventing heart-related ailments, statins have saved millions of lives since they first appeared on the market in the late 1980s.[362]

Because of their effectiveness at forestalling the most common deadly condition on Earth, statins have also come to represent a powerful financial force in the pharmaceutical industry. In 2006, physicians wrote an average of 13.1 million statin prescriptions each month.[363] One of them, Lipitor, was the most widely prescribed drug in the United States for several years.[364] In 2005, it generated $16 billion in sales derived from 144.5 million prescriptions.[365]

1. The Link Between Cholesterol and Heart Disease

The link between cholesterol and heart disease was first noted over 100 years ago.[366] Dr. Rudolf Virchow, a German pathologist, observed on autopsy that patients who died of vascular conditions in which the arteries were narrowed, like heart attacks, often had thickened and irregular artery walls.[367] He found that the arterial walls in these patients were coated with a yellowish fatty substance, which he identified as cholesterol.[368] Dr. Virchow was not able to explain the role of cholesterol in the pathological changes he observed in artery walls or how it gets there, but he raised the intriguing possibility that this kind of fat could be connected with heart disease.[369]

The first clear evidence of an association between high levels of blood cholesterol and the buildup of plaque in artery walls came from a large long-term epidemiological investigation of risk factors for heart disease

date-FINAL.pdf; John C. LaRosa et al., *Effect of Statins on Risk of Coronary Disease: Meta-analysis of Randomized Controlled Trials*, 282 JAMA 2340, 2340 (1999).

361. NAT'L INSTS. OF HEALTH, PUB. NO. 05-3290, HIGH BLOOD CHOLESTEROL 1 (2005), *available at* http://www.nhlbi.nih.gov/health/public/heart/chol/wyntk.pdf; *Cardiovascular Diseases (CVDs)*, WORLD HEALTH ORG. (Sept. 2012), http://www.who.int/mediacentre/factsheets/fs317/en/index.html#.

362. Arthur Agatston, *My 3-Point Heart Protection Plan*, PREVENTION, Nov. 2011, http://www.prevention.com/health/health-concerns/my-3-point-heart-protection-plan.

363. *Id*. at 2.

364. *See Lipitor Becomes World's Top-Selling Drug*, CRAIN'S N.Y. BUS., Dec. 28, 2011, http://www.crainsnewyork.com/article/20111228/HEALTH_CARE/111229902.

365. CONSUMER REPORTS BEST BUY DRUGS, THE STATIN DRUGS: PRESCRIPTION AND PRICE TRENDS 3 (2007), *available at* http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/Statins-RxTrend-FINAL-Feb2007.pdf.

366. Jonathan A. Tobert, *Lovastatin and Beyond: The History of the HMG-CoA Reductase Inhibitors*, 2 NATURE REVS. DRUG DISCOVERY 517, 517 (2003).

367. *Id*.

368. *Id*.

369. *See id*.

known as the Framingham Heart Study.[370] That research involved a massive effort to follow over ten thousand residents of Framingham, Massachusetts starting in 1948 to observe changes in a range of physiological markers and health outcomes over time.[371] In the 1960s, results of the research began pointing to high levels of serum cholesterol as a key culprit in the narrowing of arterial walls that could be a precursor to heart attacks.[372]

The Framingham Heart Study was the most extensive epidemiological investigation to that time.[373] The thousands of study participants received thorough physical examinations and extensive blood testing on an annual basis over the course of decades, with a cost that reached tens of millions of dollars.[374] When the project began, the benefits of this huge investment were largely speculative, as it was not possible to predict what the study would actually find.[375] This was an ideal project for government sponsorship through NIH.

The government's support for the study paid off handsomely. The most widely acknowledged result is the identification of high cholesterol as a major cause of cardiac disease, but it also identified over ten other risk factors, including salt intake and smoking.[376] Much of what is known today about heart disease and its prevention stems from this seminal research.[377]

2. The Hunt for a Way to Lower Blood Cholesterol

Once the Framingham Heart Study had fingered cholesterol as a potential killer, basic research into its molecular composition began in earnest. Scientists were particularly interested in figuring out how it is

370. Thompson, *supra* note 110, at 1671.

371. Tinker Ready, *For Sale: The Framingham Heart Study*, 6 NATURE MED. 721, 721 (2000).

372. *See* William B. Kannel et al., *Factors of Risk in the Development of Coronary Heart Disease – Six-Year Follow-up Experience: The Framingham Study*, 55 ANNALS INTERNAL MED. 33, 39 (1961).

373. *See* Cashell E. Jaquish, *The Framingham Heart Study, on its Way to Becoming the Gold Standard for Cardiovascular Genetic Epidemiology?*, 8 BMC MED. GENETICS art. 63 (2007).

374. Thompson, *supra* note 110, at 1671.

375. *Id.*

376. *Id.*; Sekar Kathiresan et al., *Clinical and Genetic Correlates of Serum Aldosterone in the Community: The Framingham Heart Study*, 18 AM. J. HYPERTENSION 657, 663 (2005); *Research Milestones*, FRAMINGHAM HEART STUDY (April 23, 2012), http://www.framingham heartstudy.org/about/milestones.html.

377. *See* Shanthi Mendis, *The Contribution of the Framingham Heart Study to the Prevention of Cardiovascular Disease: A Global Perspective*, 53 PROGRESS CARDIOVASCULAR DISEASES 10, 10-11 (2010).

synthesized in the body.[378] Blood cholesterol can come from both external and internal sources. It enters the body from the outside through dietary intake of fatty foods.[379] It is produced internally through synthesis in the liver.[380] Dietary changes alone are often effective in reducing a patient's blood level, but when they are not, controlling cholesterol's internal manufacture represents the most likely alternative approach.[381]

Research to explore the body's mechanisms of cholesterol synthesis was conducted by scientists starting in the 1940s at several universities, including Harvard, UCLA, the Max Planck Institute in Munich, and the National Institute for Medical Research in London.[382] NIH funded most of the research that was carried out in the United States.[383] The results of this work delineated the steps that lead to the liver's manufacture of cholesterol and identified a way to disrupt the process by blocking the action of a key enzyme, hydroxymethyl glutaryl coenzyme A reductase, known as HMG-CoA reductase for short.[384] The findings set the stage for a search for drugs that might serve this function.

The first challenge in finding a drug candidate was to locate a reliable source of the enzyme to use in tests.[385] In 1960, a method was devised for isolating it from baker's yeast, along with a test to determine whether a drug candidate was effective at inhibiting its activity.[386] These techniques were based on technologies that had been developed in the 1950s with support from NIH and the National Science Foundation (NSF), another federal agency that funds basic science research.[387]

With the technology in place to conduct the search, the hunt began for inhibitor molecules. In the early 1970s, it peaked the interest of private pharmaceutical firms. One company in particular, Sankyo Pharmaceuticals in Japan, devised a method for evaluating molecular candidates in molds.[388] In 1976, it found one in a species related to the strain of mold

378. *Alfred W. Alberts, Arthur A. Patchett, and Georg Albers-Schönberg*, CHEMICAL HERITAGE FOUND. (2010), http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/pharmaceuticals/restoring-and-regulating-the-bodys-biochemistry/alberts—patchett—albers-schonberg.aspx.

379. *About Cholesterol*, AM. HEART ASS'N (Aug. 14, 2012, 9:42 AM), http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/About-Cholesterol_UCM_001220_Article.jsp.

380. *Id.*

381. *Id.*

382. Thompson, *supra* note 110, at 1672.

383. *Id.*

384. *Id.*

385. *Id.* at 1672-73.

386. *Id.* at 1673.

387. Thompson, *supra* note 110, at 1673.

388. *Id.*

that produced penicillin and gave it the name compactin.[389] However, to test it on a large scale, sufficient quantities had to be produced.[390] This was accomplished using technologies that had, again, been developed with support from NIH and NSF.[391] These included x-ray crystallography and infrared and NMR spectroscopy, which are used in a range of different kinds of basic and applied research.[392]

3. A Private Manufacturer Tests the Waters

With the identification of a molecule that could block the liver's synthesis of cholesterol and the refinement of techniques to produce it in large quantities, the next step was for a pharmaceutical company to try to bring a product to market. The first to take up the challenge was Merck.[393] However, even in this commercial endeavor, it was only by collaborating with the government that success was achieved.[394]

In 1979, scientists at Merck isolated an inhibitor molecule that seemed a likely drug candidate, a substance known as lovastatin that is similar to compactin.[395] The company soon initiated clinical trials to examine its safety and effectiveness.[396] Unfortunately for the effort, at about this time, the World Health Organization reported results of a clinical trial of another new lipid lowering drug, and they were extremely disappointing.[397] There was actually a higher mortality rate for patients on the drug than for those on a placebo.[398] Then in 1980, Merck received reports suggesting that compactin could cause cancer in dogs.[399] The company's CEO, P. Roy Vagelos, who had strongly championed the quest for a cholesterol blocker, decided to terminate the clinical trials.[400]

With the private sector faltering in the quest for what promised to be a miracle drug, the government decided to step back in. Officials at the FDA began working with Merck to help it to restart its efforts.[401] While some see

389. *Id.*

390. *See id.*

391. *Id.*

392. Thompson, *supra* note 110, at 1673.

393. Suzanne White Junod, *Statins: A Success Story Involving FDA, Academia and Industry*, U.S. FOOD & DRUG ADMIN. (Apr. 13, 2009), http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SelectionsFromFDLIUpdateSeriesonFDAHistory/ucm082054.htm.

394. *Id.*

395. *Id.*

396. *See id.*

397. *Id.*

398. Junod, *supra* note 393.

399. *Id.*; Tobert, *supra* note 366, at 519.

400. Junod, *supra* note 393; P. Roy Vagelos, *Are Prescription Drug Prices High?*, 252 SCIENCE 1080, 1082 (1991).

401. *See* Junod, *supra* note 393.

the agency as a barrier that slows the process of drug development, in this case it was the instigator that kept the process going. The FDA convinced Merck to make lovastatin available to researchers at Oregon Health Sciences University and at the University of Texas.[402] Once these supplies were in the hands of academic researchers, the agency granted them permission to conduct new trials in human subjects.[403] Merck also agreed to grant the investigators access to the drug's master file, the collection of public and proprietary information on it that the company had accumulated and that was maintained by the FDA.[404]

In 1984, the gloom surrounding the prospects for statins started to lift with encouraging news on two fronts. Results of a large clinical trial released that year showed that cholesterol lowering by any means, whether dietary changes or medications, could produce a significant drop in heart disease and death.[405] And new genetic research on patients with high cholesterol succeeded in elucidating the means by which the most dangerous kind of cholesterol, LDL, is disposed of by the liver.[406] The scientists who made that discovery, Dr. Michael Brown and Dr. Joseph Goldstein, were awarded the Nobel Prize the following year.[407]

With prospects looking up for lowering cholesterol pharmacologically based on the university-based research, Merck revived its own work on lovastatin in 1983.[408] It was not long before the company had accumulated enough data to submit an application to the FDA for approval to market the drug.[409] The agency took only nine months to act on lovastatin, one of the shortest approval times up to that point.[410] Once the FDA had acted, Merck began marketing lovastatin under the brand name Mevacor in 1987.[411] It brought another statin, simvastatin, to the market at about the same time under the name Zocor.[412] By 1998, sales of Zocor had reached $4.7 billion worldwide.[413]

402. *See id.*
403. *Id.*
404. *Id.*; 21 C.F.R. § 314.420 (2012).
405. Junod, *supra* note 393.
406. *Id.*
407. *Id.*
408. Tobert, *supra* note 366, at 519.
409. *Id.*
410. Junod, *supra* note 393.
411. Rita Rubin, *Cholesterol Buster Mevacor Again Seeks OTC Approval*, USA TODAY, Dec. 9, 2007, http://www.usatoday.com/news/health/2007-12-09-mevacor_N.htm.
412. Carrie Conaway, *Too Much of a Good Thing Can Be Bad*, REGIONAL REV., Q1 2003, at 10, 16.
413. Thompson, *supra* note 110, at 1673.

Other drug companies soon got into the act, and over the next few years, several additional statins reached the market. These included Lipitor, from the Parke-Davis division of Warner Lambert, now a part of Pfizer, Pravacol from Sankyo and Bristol-Myers Squibb, and Lescol from Novartis.[414] Most of these products became blockbuster drugs, generating more than $1 billion in annual sales and serving as financial anchors for the companies that sold them.[415]

4. The Next Generation of Statins

Even with this remarkable clinical and economic success, work to improve the effectiveness of statins continued. Scientists were especially interested in finding new inhibitors of cholesterol synthesis that might be easier to produce in large quantities.[416] That work relied heavily on computer graphics programs developed at the University of California at San Diego that permitted researchers to visualize and manipulate the three-dimensional structure of molecules.[417] Previous methods of testing new drug candidates had required that they actually be synthesized, a much more expensive and time-consuming process.[418] Computer graphics allowed molecules to be vetted based on computational models.[419] The software behind this capability grew out of research funded by NSF and the Department of Defense.[420] It led to the creation of new statins that were simpler in structure and substantially cheaper to produce, including fluvastatin by Sandoz and atorvastatin by the Parke-Davis division of Warner-Lambert.[421]

Statins today are a mainstay of cardiac care and prevention. Over one-quarter of all Americans over the age of 45 take them.[422] They generate more than $30 billion in sales worldwide.[423] Lipitor has not only been the top selling drug in the world for several years but is also the world's all-time

414. *Id.*
415. *Id.* at 1671.
416. *Id.* at 1674.
417. *Id.*
418. Thompson, *supra* note 110, at 1674.
419. *Id.*
420. *Id.*
421. *Id.*
422. Alan Rappeport, *FDA Issues Warning on Cholesterol Drugs*, FIN. TIMES, Feb. 28, 2012, http://www.ft.com/cms/s/0/aaa20352-624f-11e1-872e-00144feabdc0.html#axzz1oYoFdEw1.
423. *Id.*

best-selling prescription drug with cumulative sales of more than $130 billion.[424]

Aside from their staggering economic success, statins are remarkable drugs clinically. They substantially reduce the risk of serious cardiac events, including heart attacks, an accomplishment that had only been dreamed of in the years before they were developed.[425] They have saved countless lives and incalculable costs for treating heart conditions that would otherwise have arisen.[426] These medical results have led to a financial bonanza for several pharmaceutical companies in a robust private market that would not exist without the active hand of the government.[427]

B. The Formal Approach: A Miracle in the Woods and the Development of Taxol

Statins emerged from accumulations of basic research that built up over time and increasingly pointed to clinical applications.[428] Collaborations between the public and private sectors that produced the final products evolved as the discoveries emerged. The arrangements were sometimes implicit and occasionally spontaneous.

Other drugs emerge from explicit partnerships between the government and private companies, most commonly in the form of CRADAs. Perhaps the most prominent example of a success in such an explicit collaboration is the development of Taxol, the best-selling cancer drug in history.[429] It has extended the lives of thousands of woman suffering from ovarian and breast cancer and would never have been invented but for decades of effort by government scientists and millions of dollars of investment by government agencies.[430]

1. A Search in the Forest

In 1962, Arthur Barclay, a botanist working for the United States Department of Agriculture (USDA), began an innovative field project in the Gifford Pinchot National Forest near the town Packwood, Washington, close

424. Melanie Haiken, *The Latest Statin Scare: Are You At Risk?*, FORBES, Feb. 29, 2012, http://www.forbes.com/sites/melaniehaiken/2012/02/29/the-latest-statin-scare-are-you-at-risk/; *Lipitor Becomes World's Top-Selling Drug*, *supra* note 364.

425. Thompson, *supra* note 110, at 1675.

426. Steven A. Grover et al., *The Importance of Indirect Costs in Primary Cardiovascular Disease Prevention*, 163 ARCHIVES INTERNAL MED. 333, 336, 337 (2003).

427. Thompson, *supra* note 110, at 1675.

428. *See* Zycher et al., *supra* note 3, at 108.

429. Frank Stephenson, *Research in Review: A Tale of Taxol*, FLA. STATE UNIV. OFFICE OF RESEARCH (2002), http://www.rinr.fsu.edu/fall2002/taxol.html.

430. *Id.*

to Mount St. Helens.[431] His work was part of an effort to explore the region's flora for medicinal properties.[432] The investigations led him to focus on the Pacific Yew tree, the bark of which he suspected of having a range of biological effects.[433]

Acting on his suspicions, Barclay collected and dried samples of the Yew Tree's bark and sent some to a laboratory of the USDA located in Maryland.[434] Researchers there and at NCI, a component of NIH, had become interested in screening naturally occurring chemicals as agents to fight cancer, and the agencies had entered into an agreement a few years earlier to cooperate in vetting plant samples.[435] The scientists tested Barclay's samples for a range of possible effects, and the results confirmed his initial conjecture concerning the value of Yew bark.[436] One of the tests revealed significant activity in inhibiting cancer cell cultures.[437]

Over the next several decades, Barclay's find came to revolutionize treatment for certain types of breast and ovarian cancer.[438] The fruits of his work today take the form of the drug paclitaxel, which is sold under the brand name Taxol.[439] Many consider it a wonder drug, and it is credited with extending the lives of thousands of cancer patients.[440] It was later discovered to have another, seemingly unrelated medical use as the coating for cardiac stents that hold open clogged arteries in patients with heart disease.[441]

431. *Id.*
432. *Id.*
433. *Id.*
434. Stephenson, *supra* note 429.
435. *Id.*
436. *See id.*
437. *Id.*
438. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-03-829, TECHNOLOGY TRANSFER: NIH-PRIVATE SECTOR PARTNERSHIP IN THE DEVELOPMENT OF TAXOL 5 (2003).
439. *Id.* at 1, 5.
440. Nicholas H. Oberlies & David J. Kroll, *Camptothecin and Taxol: Historical Achievements in Natural Products Research*, 67 J. NAT. PRODUCTS 129, 134 (2004); *see* Stephenson, *supra* note 429. The drug was assigned the generic name taxol upon its discovery. *Id.* In 1992, that name was trademarked, and the commercially available version became known under the brand name Taxol. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 1 n.1. The generic name was changed to paclitaxel. *Id.* From that time, references to the compound have used the generic name, while those to the commercial product use the brand name. *Id.*
441. Gregg W. Stone et al., *A Polymer-Based, Paclitaxel-Eluting Stent in Patients with Coronary Artery Disease*, 350 NEW ENG. J. MED. 221, 227 (2004).

2. Public-Private Collaboration to Produce a Drug

The story of Taxol is a tale of different sectors of the country's scientific enterprise working together under the structure that Congress had developed to promote such cooperation. After USDA's initial finding of Taxol's potential anti-carcinogenic effects, efforts began in earnest to isolate the active compound involved.[442] Research was conducted within USDA, at NCI, and at several universities and private research institutes supported by NIH grants.[443] In 1971, after almost a decade of effort, Drs. Monroe Wall and M.D. Wani of Research Triangle Institute announced that they had identified the chemical structure of the seemingly miraculous substance.[444] In 1979, researchers at the Albert Einstein College of Medicine in New York delineated the mechanism through which it works.[445]

NCI received permission from the FDA to begin clinical trials of the drug in 1982.[446] As these studies progressed through the 1980s, they increasingly pointed to effectiveness in treating the disease.[447] Final results for the second phase of the clinical trials were released in 1988 and showed a response rate of 30% among patients with the most virulent form of ovarian cancer.[448] In some tests, the rate was as high as 60%.[449] Such positive findings were unprecedented for an anti-cancer agent.[450]

Not surprisingly, Taxol's success led to a surge in demand for it.[451] However, sufficient supplies were difficult to come by. The original process for extracting Taxol required between 10,000 and 30,000 pounds of dried bark to produce one kilogram of the drug.[452] NCI estimated that in order to treat all the ovarian cancer patients who needed Taxol, 360,000 yew trees would have to be harvested every year, which made its use impractical.[453]

The answer was to create a synthetic version, and scientists in the United States, Asia and Europe labored through the 1980s toward this goal.[454]

442. Stephenson, *supra* note 429.
443. *Id*.
444. *Id*.
445. *Id*. Taxol inhibits mitosis in rapidly dividing cells, such as cancer cells. *Id*. It interferes with the beta subunit of tubulin, an important part of the microtubules that facilitate cell division. *Id*. It does this by promoting the polymerization of tubulin, which causes cell death by disrupting the normal microtubules dynamics required for cell division. *See id*.
446. Zycher et al., *supra* note 3, at 117.
447. Oberlies & Kroll, *supra* note 440, at 131 fig.1.
448. Stephenson, *supra* note 429.
449. *Id*.
450. *See id*.
451. *See id*.
452. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 12.
453. Stephenson, *supra* note 429.
454. *Id*.

Success was achieved in 1989, when researchers at Florida State University (FSU), funded by NIH, developed a process for Taxol's semisynthesis.[455] Their technique did not permit manufacture to be completed from scratch, but it enabled partial synthesis of the active ingredient.[456] Of particular importance for insuring future supplies, the raw material for the process came from a different type of yew tree that grew in much greater abundance than the one that had originally been used.[457]

The decades of effort paid off handsomely. By 1989, the government, though USDA and NCI, had discovered paclitaxel in the forests of the Northwest, isolated it, and established its clinical utility. An academic partner, FSU, had found a way to manufacture it without causing massive deforestation. With this much accomplished, NCI saw its role dwindling. It had spent over $25 million and did not have the resources for the next step, which was to produce the synthetic compound in sufficient quantities to be brought to market for large numbers of patients.[458] The government needed a partner with the wherewithal to meet this challenge.

3. Bringing a Product to Market

In 1989, soon after FSU's successful synthesis of paclitaxel, NCI solicited interest from pharmaceutical companies to enter into a CRADA to commercialize it.[459] Of the four that responded, one stood out as the most prepared for the task, Bristol-Myers Squibb (BMS).[460] In addition to extensive experience with oncology products, BMS had a track record of successful collaboration with the federal government in the development of an early treatment for AIDS.[461] To NCI, the company seemed the natural choice, and in 1991, it selected BMS for a CRADA to bring paclitaxel to market.[462] The CRADA turned out to be one of the first to result in wide availability of a breakthrough drug.[463]

Soon after NCI announced its search for a CRADA partner but before the agreement had been finalized, BMS began to explore Taxol's potential.[464] It obtained a license to use FSU's technique for semisynthesis of the drug the following year.[465] The license also applied prospectively to any

455. Zycher et al., *supra* note 3, at 117.
456. *See id.*
457. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 12.
458. Stephenson, *supra* note 429.
459. *Id.*
460. *Id.*
461. *Id.*
462. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 9.
463. *Id.* at 5.
464. *See* Stephenson, *supra* note 429.
465. *Id.*

refinements of the technology that FSU might produce, and in 1992 BMS gained the right to use a greatly improved semisynthesis technique that yielded a much larger quantity of Taxol's active ingredient.[466] This corporate-academic partnership came to benefit both parties handsomely. BMS gained the ability to market an extremely lucrative drug, and FSU received over $200 million of dollars in royalties, among the largest financial paybacks that any university had received from a technology transfer agreement up to that time.[467]

During the early years of testing, NIH performed or funded most of the clinical trials on Taxol.[468] BMS supplied the drug to NIH researchers to facilitate the trials, which had been in short supply.[469] Over the course of the CRADA, the number of research subjects participating rose from about 500 in 1989 to 28,882 at over 40 treatment centers.[470] This led to a faster pace of testing, which enabled BMS to speed the process.[471] It received approval from the FDA to market Taxol for treating ovarian cancer in December 1992, and the drug began reaching patients the following month.[472]

NIH invested a considerable amount of resources in the development and testing of Taxol both during the CRADA and after it had expired.[473] The total value of its investment before the CRADA's expiration is estimated at $183 million.[474] In the five years after the CRADA expired in 1997, it spent an additional $301 million, placing the total NIH investment at $484 million.[475] BMS provided a partial offset by supplying NIH with supplies of the drug valued at $92 million for use in the trials.[476]

BMS estimates that for its part, it spent about $1 billion in developing Taxol.[477] The return on this investment was more than adequate. By 1994, the drug had reached the market in 50 countries.[478] In 1998, sales stood at $1.2 billion, and in 2000, they peaked at $1.6 billion.[479] Through 2002, cumulative sales topped $11 billion after rising by an average of 38% a

466. *Id.*
467. *Id.*
468. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 11.
469. *Id.* at 11-12.
470. *Id.*
471. *See id.*
472. *See* Stephenson, *supra* note 429.
473. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 14.
474. *Id.* at 13.
475. *Id.*
476. *Id.* at 15.
477. *Id.* at 13.
478. *See* Stephenson, *supra* note 429.
479. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 16 tbl.1; Stephenson, *supra* note 429.

year.[480] These rewards reflected both the large demand and the high price that BMS was able to charge. In 1993, a single gram of Taxol cost $5,846.[481]

On its revenues, BMS owed NIH a royalty of 0.5% based on a license agreement that had been reached in 1996.[482] The resulting payments totaled $35 million.[483] While this was a tiny amount compared to BMS's overall returns on the drug, it was enough to repay a sizeable share of the government's investment.[484]

BMS owed some of its return on Taxol to another government source.[485] Public insurance in the form of Medicare covered the cost of the drug for most elderly patients.[486] Reimbursement totaled $687 million from 1994 to 1999, the year that a generic version of Taxol was approved.[487] And in 1999, Medicare payments represented over one-fifth of the drug's domestic sales.[488]

4. Public-Private Bargaining Over Finances

BMS entered the negotiations that led to the CRADA in a strong bargaining position. NIH needed an industry partner that could bring an adequate supply of Taxol to market.[489] When the CRADA was created in 1991, the drug was in short supply, which made clinical testing difficult.[490] None of the other companies that had responded to NIH's solicitation of

480. Stephenson, *supra* note 429.

481. *Id.*

482. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 15.

483. *Id.*

484. The size of BMS's income from Taxol has generated considerable controversy. In 1993, Senate Ron Wyden of Oregon led hearings into the drug's high price, though no Congressional action followed. Stephenson, *supra* note 429. After the CRADA expired, BMS filed patent infringement lawsuits to forestall the entry of generic competition. *Id.* This move enabled it to reap an additional $4 billion in sales. *Id.* In 2001, it was sued by attorneys general in 29 states who charged that it committed fraud in its efforts to delay the entry of generic paclitaxel in the market. *Id.*

485. BMS's success in developing Taxol based on FSU's semisynthesis technique also led to an environmental benefit. Stephenson, *supra* note 429. By 1993, the company no longer needed large supplies of Yew bark and terminated a contract for wide-scale bark collection. *Id.* Before, this, the contest between protecting forests and treating cancer had developed into a sensitive conflict. *See id.* Now, the goals no longer clashed. The company's accomplishment was recognized in 2004 with the Greener Synthetic Pathways Award from the Environmental Protection Agency. Zycher et al., *supra* note 3, at 117-18.

486. *See* U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 17.

487. *Id.*

488. *Id.*

489. *Id.* at 18.

490. *Id.* at 3.

interest ranked close to BMS in the capability to supply the drug.[491] The agency could have sought multiple partners, since CRADAs do not have to be exclusive, but this would have made the arrangement much less attractive to private partners.[492] NIH also wanted to act quickly, as the drug promised lifesaving benefits to dying patients.[493]

NIH's bargaining position was further limited by its inability to transfer rights to an actual patent.[494] Taxol did not qualify for patent protection because by the time NIH was able to file a patent application, information about the drug had already entered the public domain.[495] This negated the substance's status as "novel," a key requirement for patentability.[496] The prize it had to offer to a CRADA partner was instead access to research findings developed before and during the agreement.[497] In lieu of a patent, BMS received five years of marketing exclusivity after FDA approval of its Taxol application.[498] This functioned as the equivalent of patent protection by preventing a competitor from gaining permission to sell the same product.[499] Generic paclatxel received full FDA approval for marketing in 2000, although its status remained subject to litigation until 2002.[500]

As a result of the mismatch in bargaining strength, NIH received a rather meager level of royalties for a lifesaving drug that it was largely responsible for developing.[501] The agency is often constrained in CRADA negotiations by limited competition for participation among qualified drug companies.[502] It is unusual for more than one to express interest in a particular licensing arrangement.[503] In about 30% of cases, NIH receives no expressions of interest at all.[504] The result is that low royalties, such as the 0.5% rate negotiated with BMS, are not uncommon.[505] However, the immediate financial return to the government is a secondary concern for policy makers.

491. *See* U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 18-19.

492. *Id.* at 18.

493. *See id.* at 10 (The collaboration with BMS was "critical for BMS's quick commercialization of Taxol").

494. *Id.* at 18 (stating "NIH was unable to grant any potential partner an exclusive patent license to market paclitaxel").

495. *See* Ken Garber, *Battle Over Generic Taxol Concludes, But Controversy Continues*, 94 J. NAT'L CANCER INST. 324, 324 (2002).

496. 35 U.S.C. § 102 (2006).

497. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 18.

498. *Id.* at 10.

499. *See id.*

500. *Id.* at 28; *see also* Garber, *supra* note 495, at 324.

501. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 4, 18-19.

502. *Id.* at 20.

503. *Id.*

504. *See id.*

505. *Id.* at 4.

The central goal is to harness the innovation and drive of private companies to bring promising new technologies to patients.[506]

5. An Additional Lifesaving Use

The success of the CRADA between NIH and BMS was only part of the story. Beyond the value of paclitaxel in treating cancer, the drug also found an important use in cardiac care.[507] After the oncology benefits had been established, researchers discovered that it discourages the growth of scar tissue around the sites of metal stents that are inserted into clogged arteries to prop them open.[508] Scarring can lead to the re-deposit of clog-inducing plaque.[509]

This second use of paclitaxel was again the offshoot of a government effort, as the initial research was conducted by two scientists working at NIH.[510] Based on the finding of value in protecting the sites of cardiac stents, the agency entered into a CRADA with a company called Angiotech to commercialize this use of the drug.[511] Angiotech sublicensed its rights to Boston Scientific, which applied for FDA approval to market paclitaxel for coating cardiac stents under the name TAXUS.[512] The path to approval was eased by the drug's safety record in the previous clinical trials involving cancer treatment.[513] The product was approved for the new use, and it went on to become a clinical and commercial success, with millions of paclitaxel-coated stents sold worldwide and generating sales of over $3 billion.[514]

6. Paclitaxel and Public Policy

Paclitaxel is an example of a technology for which the CRADA system worked as its Congressional designers had intended. The government created the conditions that let the private market carry the ball in bringing a

506. *See* U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 348, at 6.

507. NAT'L INSTS. OF HEALTH, PACLITAXEL-COATED STENTS: A WAY TO BYPASS BY-PASS SURGERY 1 (2005), *available at* www.ott.nih.gov/pdfs/TaxusCS.pdf [hereinafter NAT'L INSTS. OF HEALTH, PACLITAXEL-COATED STENTS].

508. *Id.*

509. *See id.*

510. *See id.*

511. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 438, at 24.

512. *ION Paclitaxel-Eluting Coronary Stent System ,* U.S. FOOD & DRUG ADMIN. (March 7, 2012), http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm295095.htm; *Company History*, ANGIOTECH (2011), http://www.angiotech.com/about-us/company-history/.

513. NAT'L INSTS. OF HEALTH, PACLITAXEL-COATED STENTS, *supra* note 507, at 1.

514. *See Company Overview*, INNOVIA (2011), http://www.innovia-llc.com/0909/company-overview.html.

clinically important drug to patients. Through a series of laws that encouraged public-private collaboration and an initial government-funded research effort, a previously unknown substance emerged from the woods of the Pacific Northwest to become a life-saving product. The effort produced huge financial rewards for a drug company, a device company, and a university that played an instrumental role in its development. Most importantly, it has extended the lives of millions of patients around the world.

C. *The Next Era in Drug Development and the Promise of More Success Stories*

A new era in drug development dawned in the 1990s thanks to a new approach called combinatorial chemistry.[515] It permits scientists to create libraries of thousands of compounds that can be tested as candidates to perform specific functions, like inhibiting HMG CoA reductase in the liver to block the synthesis of cholesterol.[516] Within the time span of a few months, millions of such candidates can be tested for efficacy, a level of efficiency that was not previously possible.[517]

The new approach has begun to revolutionize private drug development. It is now the principal method for finding new medications of every kind, and it yields results with dramatic new speed.[518] By way of comparison, the old technology had enabled Merck to synthesize, purify and screen about 250,000 different chemicals in the 60 years between 1934 and 1994.[519] In the four years between 1995 and 1999, using combinatorial chemistry techniques, it synthesized and tested 4.5 million.[520]

Like so many other technological advances that have bolstered the financial prospects of private pharmaceutical companies, combinatorial chemistry was devised by scientists who relied on NIH for financial support.[521] Beyond the pharmaceutical manufacturers that use it, a burgeoning new industry now supports its application. A raft of companies provides instrumentation, chemical re-agents, and software.[522] Through them, the government investment in advancing the process of drug development has sent ripples through a large swath of the private sector.[523]

515. Thompson, *supra* note 110, at 1675.
516. *Id.* at 1672, 1675.
517. *Id.* at 1675.
518. *Id.*
519. *Id.*
520. Thompson, *supra* note 110, at 1675.
521. *Id.*
522. *Id.*
523. *See id.*

VI. THE "FREE-MARKET" PHARMACEUTICAL INDUSTRY AND THE GOVERNMENT

A. What Would the Industry Look Like Without the Government?

Let us turn to the fundamental question that underlies this article. How did the pharmaceutical industry, which has remained among the most profitable for decades, get that way? Certainly, entrepreneurship and innovation played a tremendously important part in maintaining the robustness of drug companies over the years. Market forces continuously prod private companies to devise new products and stay ahead of the competition. However, those companies must have raw materials to work with in their intellectual arsenal. For pharmaceutical firms, that is basic knowledge of human biology. Over the past three-quarters of a century, the greatest producer of that knowledge by far has been the United States government.

We can highlight the government's role in creating and maintaining the pharmaceutical industry by asking what the industry would look like without its government base. Without question, it would still exist. Pharmaceuticals date back almost as far as recorded history.[524] Ancient Egyptian writings describe pharmaceutical preparations, as do the records of almost every early civilization.[525] Private companies, as well as individuals, have been manufacturing drug products since colonial times in America, long before there was an NIH to support research or an FDA to oversee quality.[526]

But what would that industry look like without the pillars of government support that emerged in the twentieth century? It would almost certainly be a shadow of its present self. Virtually every major drug that has supported private pharmaceutical profits over the past 50 years was developed with government support in one form or another. In no field of medicine would available treatments approach the range or effectiveness that they do today. Imagine cardiac care without statins, oncology care without paclitaxel, or care for AIDS without AZT. In fact, it is impossible to name any medical specialty that does not today depend for its pharmacological tools, in some cases almost entirely, on investment by the government and the innovation it spawned.

524. *See* Renate Germer, *Ancient Egyptian Pharmaceutical Plants and the Eastern Mediterranean*, in THE HEALING PAST: PHARMACEUTICALS IN THE BIBLICAL AND RABBINIC WORLD 69, 69-71 (Irene Jacob & Walter Jacob eds., 1993).

525. *Id.*

526. *See* Renate Wilson & Woodrow J. Savacool, *The Theory and Practice of Pharmacy in Pennsylvania: Observations on Two Colonial Country Doctors*, 68 PENN HISTORY 31, 35 (2001).

B. Could Private Industry Have Made It on Its Own?

We know what the government has contributed, but it would also be fair to ask whether the industry might have accomplished these or similar advances on its own. Without NIH, might private entrepreneurs have mustered the resources to meet the basic science challenges that created modern medicine? Perhaps the same market forces that promote applied research in bringing products to market could have supported the advances in biology that underlie it.

To answer that question, we can look to the stories behind some of the most important fruits of government intervention. Merck was ready to give up on statins before NIH and the FDA stepped in with a helping hand.[527] Government scientists combed the forests of the Pacific Northwest in search of anti-carcinogens, eventually discovering paclitaxel, at a time when private companies showed little interest.[528] And beyond these examples, the development of countless other drugs tells a similar tale.[529]

As we look to the future of medicine, we can ask whether any private company could have devoted the resources to mapping the human genome, the essential first step in opening the door to genetic medicine. The investment required was huge and the knowledge gained will require decades to commercialize. Moreover, its findings are public information available to everyone, including competing companies, to take advantage of.[530] What private investors would have allowed their funds to be used in this way?

C. Has the Government Acted Wisely?

Government support for the pharmaceutical industry has its share of critics. Many see the large amounts of money that are given as an undeserved subsidy for an industry that could be amply profitable on its own.[531] They point in particular to companies that patent discoveries based on NIH-funded research, thereby staking an ownership claim in a publicly funded resource.[532] They ask why private ventures should be allowed to reap

527. Junod, *supra* note 393.

528. Stephenson, *supra* note 429.

529. *History of the Human Genome Project*, *supra* note 160. Two examples of important drugs whose development relied heavily on NIH support for basic research are beta blockers, which treat high blood pressure among other conditions, described in Zycher et al., *supra* note 3, at 107, and Havrix, a vaccine against Hepatitis A, described in NAT'L INSTS. OF HEALTH OFFICE OF TECH. TRANSFER, HAVRIX WAGING WAR AGAINST A COMMON ENEMY: A CASE STUDY (2002), *available at* www.ott.nih.gov/pdfs/HavrixCS.pdf.

530. *Major Events in the HGP*, *supra* note 164.

531. *See* Jackie Judd, *Taxpayers End Up Funding Drug Companies*, ABC NEWS, June 7, 2012, http://abcnews.go.com/WNT/YourMoney/story?id=129651.

532. *Id.*

such rewards, when taxpayers supported the underlying scientific advances.[533]

CRADAs can result in particularly disproportionate returns for private participants. In the case of Taxol, NIH received $35 million on behalf of taxpayers under a licensing agreement with BMS after spending almost $500 million to test the drug.[534] By the time it first faced generic competition, BMS had earned over $11 billion.[535] The company claimed that it invested $1 billion of its own money in applied research to bring Taxol to market, but even with this expense, its rate of return dwarfed that of NIH.[536] Is it fair that a private entity should profit so handsomely from an invention that would not have been possible without substantial government investment?

Tax subsidies for research and development often come in for especially harsh criticism.[537] Do highly profitable companies really need a subsidy to invest in research, when they would have to make the investment anyway to remain competitive? Perhaps the government already gives the industry enough research support through NIH.

FDA oversight of safety is also often questioned as too lax.[538] Several drugs with dangerous side effects have slipped through the vetting process, sometimes after receiving accelerated review.[539] The result has been recalls and additional warnings after reports of patient harm.[540] Vioxx, for example, was approved on an expedited basis as a treatment for arthritic pain, and its

533. Judd, *supra* note 531.

534. Stacye Bruckbauer, *Capitalizing on Commercialization: Should Congress Revisit the Bayh-Dole Act?*, 95 J. NAT'L CANCER INST. 1429, 1429 (2003).

535. Stephenson, *supra* note 429. Competition from a generic version of Taxol was delayed for over four years because of patent challenges by BHS. *See* Garber, *supra* note 495, at 324.

536. Bruckbauer, *supra* note 534, at 1429.

537. *See e.g.*, Donald W. Light & Joel R. Lexchin, *Pharmaceutical Research and Development: What do we Get for all that Money?*, 345 BRITISH MED. J. e4348 (Aug. 7, 2012) (arguing that drug companies use the tax subsidies, as well as other public financing, as a part of their business model that results in net after-tax profits that are "substantially higher than profits for all other Fortune 500 companies").

538. *E.g.*, U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-09-866, NEW DRUG APPROVAL, FDA NEEDS TO ENHANCE ITS OVERSIGHT OF DRUGS APPROVED ON THE BASIS OF SURROGATE ENDPOINTS 35 (2009).

539. *Id.*; *see* Thomas J. Moore & Curt D. Furberg, *The Safety Risks of Innovation: The FDA's Expedited Drug Development Pathway*, 308 JAMA 869, 869-70 (2012).

540. Moore & Furberg, *supra* note 539, at 869-70.

review failed to spot long-term cardiac hazards that a more deliberative process might have revealed.[541]

Perhaps taxpayers could be getting a better deal from their investment in the private pharmaceutical industry. The system of support could undoubtedly be improved in many ways. However, whatever the optimal level of support, government investment has over the years been, and remains today, crucial to the industry's wellbeing. Whatever shortcomings the system may have, we have clearly gotten a robust and highly profitable set of companies and a cascade of new drugs in return for the government's involvement. The pharmaceutical industry would not exist in the form it takes today, with all of its accomplishments and faults, but for a hundred years of government intervention.

D. Conclusion: Public Investment and Private Industry

Pharmaceuticals are developed, manufactured, sold, and distributed in the United States through the private sector. Private investment and competition among firms drive the sector's economics. These dynamics characterize what is typically thought of as a "free-market." However, the market does not exist because the government stepped aside and let private enterprise operate without constraint. Quite to the contrary, it operates precisely because the government has insinuated itself into almost every aspect of the business.

541. *Vioxx (rofecoxib) Questions and Answers*, U.S. FOOD & DRUG ADMIN. (Sept. 30, 2004), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatients andProviders/ucm106290.htm.