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Michael J. Malinowski

Louisiana State University Law Center, mjmalin@lsu.edu

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51 U. Louisville L. Rev. 101

University of Louisville Law Review

2012

Articles

*101 GOVERNMENT RX-BACK TO THE FUTURE IN SCIENCE FUNDING? THE NEXT ERA IN DRUG DEVELOPMENT

Michael J. Malinowski [FNa1]

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We shall not cease from exploration [a]nd the end of all our exploring [w]ill be to arrive where we started [a]nd know the place for the first time.

-T.S. Eliot [FN1]

I. Introduction: 5:30 AM, Monday, July 16, 1945

[T]he atomic age began. While Manhattan staff members watched anxiously, the device exploded over the New Mexico desert, vaporizing the tower and turning asphalt around the base of the tower to green sand. The bomb released approximately 18.6 kilotons of power, and the New Mexico sky was suddenly brighter than many suns. Some observers suffered temporary blindness even though they looked at the brilliant light through smoked glass. Seconds after the explosion came a huge blast, sending searing heat across the desert and knocking some observers to the ground. A steel container weighing over 200 tons, standing a half-mile from ground zero, was knocked ajar. . . . As the orange and yellow fireball stretched up and spread, a second column, narrower than the first, rose and flattened into a mushroom shape, thus providing the atomic age *102 with a visual image that has become imprinted on the human consciousness as a symbol of power and awesome destruction. [FN2]

The uranium atom was split successfully in early 1939. [FN3] Fearing that the Nazis could and would develop an atomic bomb, the United States undertook the Manhattan Project to preempt the threat to the very existence of democratic society. [FN4] The Project was a massive federal government hands-on undertaking—a science research and development (“R&D”) mission that orchestrated establishment of several laboratories at sites across the United States, an army of researchers, and input from industry, most notably DuPont and the Kellogg Company. [FN5]

During the remainder of the twentieth century, U.S. investment became a concerted effort to promote both the advancement of science through academia and American global economic competitiveness. [FN6] This duality served the United States well given that industry and academia did not share a science culture at the time and tended to remain separate. [FN7] The U.S. government acted as an intermediary and invested to advance science on both fronts. [FN8] Former President Eisenhower recognized this rite of passage and its implications and shared his vision in a farewell address he delivered through a radio and television broadcast on January 17, 1961:

[R]esearch has become central; it also becomes more formalized, complex, and costly. A steadily increasing share is conducted for, by, or at the direction of, the Federal government.

....

The prospect of domination of the nation's scholars by Federal employment, project allocations, and the power of money is ever present and is gravely to be regarded. Yet, in holding scientific research and discovery in respect, as we should, we must also be alert to the equal and *103 opposite danger that public policy could itself become the captive of a scientific-technological elite. It is the task of statesmanship to mold, to balance, and to integrate these and other forces, new and old, within the principles of our democratic system-ever aiming toward the supreme goals of our free society. [FN9]

As discussed in detail in Part II, subsequent to the Manhattan Project, three distinguishable eras of U.S. government science funding have unfolded. [FN10] In prescription drug development, with its enormous human health and economic implications, much reliance has been placed upon industry. [FN11] Industry has taken responsibility for the vast majority of clinical research and drug distribution and marketing, while the U.S. government has generously funded basic (bench) research, largely through the National Institutes of Health ("NIH") and National Academy of Sciences ("NAS"). [FN12] Among governments, the United States remains the lead global financial investor and producer of biomedical R&D by a wide margin. [FN13]

Unfortunately, the United States has sunk into a drug development dilemma, which is addressed in Part III. Government funding of basic research has gifted industry with resources for drug R&D, including a map *104 of the human genome. [FN14] Nevertheless, as observed by Dr. Francis Collins, Director of the NIH, the drug industry's "productivity has been declining for fifteen years" and shows no signs of improving. [FN15] This Article proposes that the federal government respond to the drug development dilemma by, in the spirit of the Manhattan Project and Human Genome Project ("HGP"), reducing reliance on industry and substantially expanding the presence of both NIH and the Food and Drug Administration ("FDA") in human clinical research.

II. Science Funding: The U.S. Legacy [FN16]

“The threat of annihilation of democratic society during World War II . . . by advances in technology inspired tremendous U.S. investment to raise the base of science.” [FN17] The United States continued and increased its investment, other governments did the same and, as explained below, government involvement matured into our present, shared research establishment-with the fulcrum for drug development resting heavily on industry and commercialization. [FN18] This evolution unfolded in three eras distinguishable by their origins and nature: the military-industrial complex (“MIC”) era (1939 to the present); an era of academia-industry separation *105 (mid-1940s into the 1980s); and an era of government-academia-industry integration which commenced in 1980 and extends into the present. [FN19]

A. The Military-Industrial Complex Era

The MIC era grew out of World War II (“WWII”). The United States entered WWII without a standing army and with little meaningful infrastructure to manufacture military weapons. [FN20] The war effort imposed a focus on application in science and technology, and the U.S. government became a contract purchaser and financier of invention by both academia and industry. [FN21] The United States left WWII with established, expansive, and ongoing relationships with industry and academia. [FN22] Generally, the flow of federal funding shifted into relationships with industry to build the MIC and into separate university grant funding-academic research, meaning research for the sake of research rather than more immediate commercial application. [FN23] The latter was advanced immensely through *Science: The Endless Frontier*, [FN24] a 1945 report to President Truman from Vannevar Bush, Director of the Office of Scientific Research and Development. “Its main goal was to recommend establishing the United States Office of Research and Development, which in time morphed into the National Science Foundation (NSF) and NIH, chiefly to fund the basic research needed to undergird the full range of applied sciences.” [FN25] Financial support of the same became a permanent major expenditure and budget priority. [FN26] The MIC continued, just as President Eisenhower predicted, and raged in the decades following his farewell address, culminating in today’s “War on Terror.” [FN27]

*106 B. Era of Academia-Industry Separation

The era of separation between academia and industry was facilitated by a duality in federal funding. To the side of MIC funding, most research grants to universities were issued through review by academic peers to promote research for the sake of advancing science, largely removed from any serious consideration of application. [FN28] University researchers applied for the same. [FN29] Industry was concerned about commingling their research investments with universities’ for fear of government

claims to resulting inventions. [FN30] This division remained until the 1980s, [FN31] which reinforced a separation between academia and industry in science research. [FN32]

MIC continued on: the 1950s and early 1960s were dominated by the Cold War and a series of confrontations centered on science-Sputnik 1, launched on October 4, 1957, followed by the Bay of Pigs Invasion, the Cuban Missile Crisis, and placement of man on the moon, all of which increased demands that federally funded science produce tangible applications. [FN33] The federal government grew impatient with academic research and diminished its funding. [FN34] “The annus horribilis, 1968, brought an end to the expansion of academic research and anguish over the role that the university had assumed.” [FN35] While universities served as bastions for *107 anti-government protests, government and public sentiment soured further. [FN36] The 1970s proved a challenging decade for academia as government decided to give much less. [FN37]

C. Era of Integration Among Government, Academia, and Industry

Integration among government, academia, and industry was a phenomenon of the 1980s. By the end of the 1970s, the country faced double-digit unemployment. [FN38] A severe oil shortage necessitated harsh rationing and caused prices at the pump to skyrocket. [FN39] The country was in an economic crisis, and the public was frustrated with both big government and big business. [FN40] Demand for more R&D and economic stimulus grew deafening. [FN41] Congress was shoved into action. [FN42] Taxpayer investment in academic research was not leaving university filing cabinets, and legislation was enacted to bust them open to help stimulate the economy. [FN43] Specifically, Congress enacted legislation that put into motion an intense academia-industry science policy that, through globalization, has impacted the world's science norms. The primary pieces of legislation, both enacted in 1980, are the Bayh-Dole Act [FN44] and the Stevenson-Wydler Act: [FN45]

*108 The legislative intent of Bayh-Dole was, through reform of patent policy related to government-sponsored research: (1) to enable and encourage universities, not-for-profit corporations, and small businesses to patent and commercialize their federally-funded inventions and (2) to allow federal agencies to grant exclusive licenses for their technology to provide more incentive to businesses. [FN46]

The net result is a “give away” of invention created with federal taxpayer dollars for commercial application, which has integrated government, academia, and industry in science research. [FN47] This policy effectively “unlocked all the inventions and discoveries that had been made in laboratories throughout the U.S. with the help of taxpayers' money.” [FN48] The impact on research institutions, researchers, and science itself has been profound: “A fruitful collaboration between academic researchers and industry promised to fuel not only economic development but also new sources of revenue for universities. A vast movement of privatization was underway by the mid-1980s, and it reinvigorated research universities.” [FN49]

From the 1990s onward, government, academia, and industry have integrated with explosive intensity, “giving rise to all the benefits, concerns, *109 and controversies that accompany such dramatic and rapid change.” [FN50] As stated by one observer, “It has turned universities into commercial entities, created a multibillion-dollar industry of technology transfer, and subsidized virtually every biotechnology company and discovery of the past twenty-five years.” [FN51] The integration has gone global. [FN52]

III. The Drug Development Dilemma

Drug development has made a profound impact on human health. As recognized by Dr. Marcia Angell, former Editor in Chief of the New England Journal of Medicine and vocal critic of today's drug industry:

No one would want to be without, say, insulin for diabetes, antimicrobial agents to fight infections, vaccines to prevent a host of serious diseases, anticoagulating agents to treat heart attacks, chemotherapy for cancer, a panoply of effective painkillers and anesthetics, and many others. Gleevec is a major advance, as are Epogen and Taxol. Prilosec is important, too, as are statins and ACE inhibitors and many other drugs. All of these agents have extended and greatly improved our lives. [FN53]

Moreover, although the secrecy of data makes the cost of developing new drugs mere estimations, it is beyond dispute that the endeavor is extraordinarily expensive and time-consuming, and the clinical failure rate is towering—approximately 80%. [FN54] Industry has invested enormously in recent years—for example, \$45.8 billion in 2009. [FN55] The U.S. government also has invested tens of billions of dollars annually: the NIH budget *110 continues to hover at approximately \$30.9 billion annually, [FN56] and tens of billions in taxpayer dollars have been invested annually since the 1990s. [FN57]

Despite these accomplishments, enormous industry and government investment in basic research, [FN58] and the infusion of scores of research-enabling technologies in recent years, most notably the map of the human genome, [FN59] overall drug development has sunk into a state of doldrums—a fifteen-year slump. [FN60] Shockingly, in 2010, Pfizer Inc., the world's largest research-based pharmaceutical company, did not secure a single new drug approval. [FN61] “The bottom line has been a 45 percent decline in the company's share price between 2000 and 2005. Unfortunately, many of the likely replacements are targeted for niche markets that cannot possibly generate the sales of the huge products that preceded them.” [FN62] Discouraged, large drug makers are investing less: [FN63]

TABULAR OR GRAPHIC MATERIAL SET FORTH AT THIS POINT IS NOT DISPLAYABLE

*111 In addition, the perception of the public and many in the medical profession of the pharmaceuticals on the market is grossly inflated. Though most of those in need of health care want to believe wholeheartedly in pharmaceuticals, prescription drugs generally are unpredictable: a mere one-third act as expected when prescribed to patients. [FN64] This uncertainty *112 “exposes patients to potentially harmful drug interactions and delays potentially effective or the ‘right’ treatment.” [FN65]

Also, adverse drug reactions cause more than two million hospitalizations each year and 100,000 deaths. [FN66] In fact, the United States experiences more deaths from the legal use of prescription medications than from automobile accidents. [FN67] The poor performance of drugs already on pharmacy shelves contributes to the fact that medicine remains much more of an art than a science:

Even today, with a high-tech health-care system that costs the nation \$2 trillion a year, there is little or no evidence that many widely used treatments and procedures actually work better than various cheaper alternatives.

....

... And while there has been progress in recent years, most of these physicians say the portion of medicine that has been proven effective is still outrageously low-in the range of 20% to 25%. [FN68]

*113 Poor drug performance has shaken confidence in the FDA and triggered congressional action, [FN69] scathing reports from the Government Accountability Office and the Institute of Medicine, [FN70] and class action litigation, underscoring that drug development is in a problematic state and certainly not living up to its potential. [FN71] The FDA had to withdraw ten of its approved drugs for safety concerns between 2000 and March 2006, [FN72] and “[i]t has been estimated that as many as half of all new drugs have at least one serious adverse effect that is unknown at the time of drug approval.” [FN73] Vioxx is a notorious agency mistake-“a ‘scarlet letter’ the FDA is likely to wear for years to come.” [FN74] More mistakes were admitted in the fall of *114 2010. [FN75] The FDA “concluded that in some cases two types of drugs that were supposed to be preventing serious medical problems were, in fact, causing them.” [FN76] Specifically, Avandia, prescribed heavily to treat type-2 diabetes, was associated with an increased risk of heart attacks and strokes-a serious problem for the target patient group given that two-thirds of diabetics die of heart problems. [FN77] Bisphosphonates, prescribed to prevent bone loss, was determined to actually cause thigh bone fractures and jawbone degeneration. [FN78] Again, frustrated, industry is paring back on research and channeling its funds into marketing. [FN79] It has outsourced clinical research to contract research organization (“CRO”) bean counters, who just make the data needed for approval happen. [FN80] Yet, in recent years government has increased dependence on industry to get clinical research done. [FN81]

*115 IV. A Law-Policy Fix for the Drug Development Doldrums

Many commercial drug developers and their supporters claim that the drop off in new drug approvals is due to over-regulation. [FN82] In fact, the opposite is true: industry is clinging to the low science and regulatory standards of the past, making bad and expensive decisions based upon these low standards, stretching the commercial lives of pharmaceuticals through manipulation of the patent system, and contriving “me too” drugs rather than engaging in genuine innovation. [FN83]

Lax regulatory standards introduced in 1997 under the FDA Modernization Act (“FDAMA”) have enticed industry to engage in a race to the bottom. [FN84] Section 506B of FDAMA introduced a presumption in *116 favor of market approval contingent on follow-up studies, [FN85] which the FDA has not been enforcing and industry has not been performing. [FN86] This presumption is misplaced given that drug sponsors exercise extensive control over the content of new drug applications, [FN87] and the standard for market approval is to just outperform a placebo-meaning to be better than *117 nothing-with tolerable adverse events. [FN88] Once drugs reach pharmacy shelves, physicians have the discretion to prescribe them off-label regardless of the limitations of the data that put them on the market. [FN89] The approval process does not include head-to-head comparisons between new drugs and those already on the market. [FN90]

The quantity and scale of clinical trials underway today is unprecedented-a reflection of the desperation of the biopharmaceutical sectors to replenish their revenue streams. [FN91] Clinical research is highly susceptible to manipulation. [FN92] As observed by Dr. Angell, “Trials can be rigged in a dozen ways, and it happens all the time.” [FN93] The so-called gold standard for generating clinical data is group design, which produces mathematical abstracts (probabilities) that represent the group under study as a whole, but not necessarily any individuals used to trigger the data. [FN94] Moreover, clinical research has been shifted from academic medical centers to commercial service providers- CROs. [FN95] An academic check on the *118 integrity of clinical research, the public nature of research promoted through the involvement of academia, has been lost. [FN96]

As Dr. Angell explains:

Until the 1980s, researchers were largely independent of the companies that sponsored their work. Drug companies would give a grant to an academic medical center, then step back and wait for faculty researchers to produce the results. They hoped their product would look good, but they had no way of knowing for sure. They certainly did not attempt to tell the researchers how to run their clinical trials. Now, however, companies are involved in every detail of the research-from design of the study through analysis of the data to the decision whether to publish the results. That involvement has made bias not only possible but extremely likely. Researchers don't control clinical trials anymore; sponsors do. [FN97]

*119 When academic medical centers are involved, they often hold equity interests in research outcomes. [FN98] Many senior NIH scientists also hold financial entanglements in research outcomes. [FN99] The norm has become commercial controls on publication and a loss of data transparency. [FN100]

Although the biopharmaceutical sectors maintain an army of lobbyists in the nation's capital, [FN101] disappointment with drug development has inspired law-policy interventions. Congress enacted the Food and Drug Administration Amendments Act of 2007, which demands more scrutiny for market approval, extensive surveillance of pharmaceuticals on the market with a focus on health care outcomes, and dissemination of much more information to health care providers. [FN102] Also, regulations to protect human subjects are finally being revisited. [FN103]

Still, more meaningful government intervention is needed to align drug development with its potential and to break through the existing doldrums. In the spirit of the Manhattan Project and HGP, the federal government should undertake clinical research and lessen reliance on industry for *120 advanced drug development. [FN104] There is some movement in this direction. Dr. Francis Collins, leader of the U.S. government's HGP effort and Director of the NIH, has proposed direct government involvement to convert the map of the human genome into human health benefits. [FN105] Specifically, he has proposed a National Center for Advancing Translational Sciences (“NCATS”) to lift the drug development industries out of their steep fifteen-year slump. [FN106] “The central role for the proposed Center would be to establish and provide focused, integrated, and systematic approaches for building new bridges that link basic discovery research with therapeutics development and clinical care.” [FN107] The NIH is dissolving one of its twenty-seven existing entities to form NCATS and provide approximately \$1 billion in funding. [FN108] According to Janet Woodcock and her co-authors, there is new-found appreciation for the fact that “[i]nnovative drug development requires science and regulation to advance in concert. Nowhere is this need more apparent or urgent than in *121 the development of combination therapies.” [FN109] Contemporary genetics is about understanding disease pathways rather than just eliminating symptoms, and specialty care is emerging as a dominant focus in new drug approvals and patient treatment. [FN110]

The federal government is moving in the right direction with NCATS, but it must go beyond basic (bench) science and plunge into clinical research. Obviously, the commercial sector is not rising to the occasion-it is not producing in spite of the proliferation of enabling technologies bequeathed to it through HGP and extraordinary investment. [FN111] The biopharmaceutical sectors have tremendous potential they simply are not realizing. [FN112]

Just as the U.S. government intervened successfully in science to preempt Nazi competitors in the creation of the atomic bomb and more recently to complete a map of the human genome, the biology counterpart to the periodic table that evolves science into penetrating disease pathways, the United States must intervene in clinical research to boost drug development. [FN113] The NIH and FDA should work jointly in the endeavor given their distinguishable but complementary science focuses and staff skill sets.

The FDA has precedent to intervene in clinical research independent from commercial sponsors. Through the Best Pharmaceuticals for Children Act, Congress enabled the agency to get pediatric studies done in spite of industry resistance. [FN114] The Act established a trust fund, which the FDA draws from to contract with third parties to accomplish the studies needed. [FN115] There also is NIH precedent. The NIH has made contributions that have directly facilitated private sector drug development, including the Molecular Libraries Program, the Therapeutics for Rare and Neglected Diseases Program, the Rapid Access to Interventional Development *122 Program, and the Clinical and Translational Science Awards Program. [FN116] This precedent is a foundation for the FDA and NIH to build upon and contribute to human health.

Professor Epstein cautions against the infusion of new regulatory standards and expansion of the role of government in drug development:

No way exists for government, try as it may, to take the lead in developing new commercial processes. Likewise, no way exists for government to take over the task of ensuring that all individuals receive the safest and most effective care, or even to set by edict some minimum threshold with which all private firms must comply. The implicit paternalism of the FDA and the tort system hurts the very people it is intended to help. [FN117]

Henry Miller shares Professor Epstein's sentiment that the U.S. government should leave drug development to the private sector, and he opposes NCATS: "Government bureaucrats are rarely leaders of technological innovation. They are not qualified to act as venture capitalists in choosing the most promising and deserving commercial product to fund and develop." [FN118]

The thrust of Professor Epstein's position is that, in drug development, the low-hanging fruit has been picked and a slump was inevitable:

I stated at the outset of this book that it is hard to return the pharmaceutical industry to its glory days of fifty or sixty years ago. In the interim we have gathered all the low-hanging fruit. But the current challenge is not whether we can recreate the heady optimism of Vannevar Bush's 1945 praise of The Endless Frontier, any more than it is whether we can make the California gold rush last forever. [FN119]

*123 Reality is that genomics and related disciplines (proteomics, bioinformatics, pharmacogenomics, and pharmacogenetics, to name just a few) have seeded new orchards with acreage that melts deeply into the distant horizon-adding dimensions of potential to the frontier of drug development. The drug development past, just taking away symptoms without understanding disease pathways, fortunately is not a reflection of the present and future. Genomics, the study of genetic expression, has introduced a new beginning, and there is an obligation to embrace it in drug development and to contribute as meaningfully as possible to human health. People's lives depend upon it-literally. The U.S. government must rise to the occasion and expend the resources necessary to better align drug development with its potential.

V. Conclusion

Reliance on government to solve dilemmas is not popular at this time, but in science, the U.S. government has a legacy of rising to the occasion. We need another intervention. This Article has embraced NCATS and proposed that more direct government involvement in human clinical research is necessary to lift drug development out of its doldrums. We already have made such an investment through HGP, and so much human life is at stake. Lost opportunity and, to say the least, disappointing performance for a sector that impacts all levels of human health and the national economy so fundamentally demands a government intervention in the spirit of the Manhattan Project and HGP. Industry pushed completion of the map of the human genome, but it did so by drawing from the public domain and working off of what the government effort had accomplished-the intellectual property

placed in the public domain. The government's efforts also inspired a bountiful bouquet of enabling technologies along the way, from gene sequencing capabilities to DNA chips, that have enabled the global biotechnology sector. The project never would have been started without the U.S. government making a decision to fund it from 1988 to 2003 with a \$3 billion investment. [FN120]

It is time to move forward, and to make medical sense out of the map of the human genome and the universe of enabling technologies the effort has inspired. Drug development is off track, dismally so, and a government intervention is essential to reach the potential already framed by the vested government investment in the map of the human genome. It is time to *124 move forward and embrace the opportunity to improve human health introduced through contemporary genomic science.

[FN1]. Michael Malinowski is the Ernest R. and Iris M. Eldred Professor of Law, Paul M. Herbert Law Center, Louisiana State University. He received his J.D. from Yale Law School, where he was an Articles Editor for the Yale Law Journal, and his B.A., summa cum laude, from Tufts University. This Article is the fourth in a series of recent articles addressing the prescription drug research and development and delivery problems: Doctors, Patients, and Pills-A System Popping Under Too Much Physician Discretion? A Law-Policy Prescription to Make Drug Approval More Meaningful in the Delivery of Health Care, 33 *Cardozo L. Rev.* 1085 (2012); Drug Development- Stuck in a State of Puberty?: Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability, 56 *St. Louis U. L.J.* 363 (2012) (co-author Grant G. Gautreaux); All That Is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global "Gold Standard" for Drug Research and Development, 45 *Cornell Int'l L.J.* 185 (2012) (co-author Grant G. Gautreaux). The author appreciates the editorial contributions of and enjoyable experience created by Lauren Claycomb and the other editorial staff of the University of Louisville Law Review.

[FN1]. T.S. Eliot, *Little Gidding*, in *Four Quartets* 31, 39 (Mariner Books 1968) (1943).

[FN2]. F. G. Gosling, U.S. Dep't of Energy, *The Manhattan Project: Making the Atomic Bomb* 48 (1999), available at http://energy.gov/sites/prod/files/edg/media/Making_Atomic_Bomb.pdf; see Atomic Heritage Found., *The Manhattan Project: The Birth of the Atomic Bomb in the Words of Its Creators, Eyewitnesses, and Historians* 294-313 (Cynthia C. Kelly ed., 2007).

[FN3]. *The Manhattan Project*, U.S. History, <http://www.ushistory.org/us/51f.asp> (last visited Aug. 12, 2012).

[FN4]. Gosling, *supra* note 2, at vii.

[FN5]. *The Manhattan Project*, Atomic Heritage Found., <http://www.atomicheritage.org/index.php/veterans/45-the-manhattan-project.html> (last visited Aug. 12, 2012); see Gosling, *supra* note 2, at 28-29; Richard Rhodes, *The Making of the Atomic Bomb* 431 (1986).

[FN6]. Owen C.B. Hughes, Alan L. Jakimo & Michael J. Malinowski, *United States Regulation of Stem Cell*

Research: Recasting Government's Role and Questions To Be Resolved, 37 Hofstra L. Rev. 383, 389-400 (2008).

[FN7]. See id. at 390.

[FN8]. See id. See generally Atomic Heritage Found., supra note 2.

[FN9]. President Dwight D. Eisenhower, Farewell Radio and Television Address to the American People (Jan. 17, 1961), available at <http://www.presidency.ucsb.edu/ws/index.php?pid=12086&st=&st1=>. See generally Jesse Smith, Introduction to The Military-Industrial Complex, The Farewell Address of President Eisenhower 3, 3-8 (2006).

[FN10]. Michael J. Malinowski, Keynote Address, A Law-Policy Proposal to Promote the Public Nature of Research in Contemporary Life Science, 39 Biennial Rev. Law, Sci. & Tech. 1, 2-9 (2009) (presented at "A Discourse on the Public Nature of Research in Contemporary Life Science," hosted by Academia Sinica, Taipei, Taiwan); see also Hughes, Jakimo & Malinowski, supra note 6, at 387.

[FN11]. See generally Kathleen M. Boozang et al., Ctr. for Health & Pharmaceutical Law & Policy, Seton Hall Univ. Sch. of Law, Conflicts of Interest in Clinical Trial Recruitment & Enrollment: A Call for Increased Oversight (2009), available at http://law.shu.edu/ProgramsCenters/HealthTechIP/upload/health_center_whitepaper_nov2009.pdf.

[FN12]. Gardiner Harris, A New Federal Research Center Will Help Develop Medicines, N.Y. Times, Jan. 22, 2011, at A1, available at <http://www.nytimes.com/2011/01/23/health/policy/23drug.html?pagewanted=all> ("The National Institutes of Health has traditionally focused on basic research, such as describing the structure of proteins, leaving industry to create drugs using those compounds."). See generally Marcia Angell, The Truth About Drug Companies 22, 30 (2004); Inst. of Med. of the Nat'l Acads., Accelerating the Development of New Drugs and Diagnostics: Maximizing the Impact of the Cures Acceleration Network, Workshop Summary (2012), available at http://www.nap.edu/openbook.php?record_id=13452&page=R1; Boozang et al., supra note 11, at 6.

[FN13]. See Titus Galama & James Hosek, U.S. Science Is Holding Its Own: Despite Cries of Alarm, We Remain the Global Leader in Innovation, Pittsburgh Post-Gazette, July 9, 2008, at B7, available at <http://www.post-gazette.com/stories/opinion/perspectives/us-science-is-holding-its-own-401532/> ("Although China, India and South Korea are starting to account for a significant portion of the world's science and technology activities, and are showing rapid growth, they still account for a very small share of patents, science publications and citations.").

[FN14]. Human Genome Project Information, genomics.energy.gov, http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml (last updated July 31, 2012). The Human Genome Project ("HGP") map was an international odyssey to identify the shared common denominator

among human beings at the genetic, molecular level. *Id.* HGP was the most ambitious federal government science undertaking since the Manhattan Project and moon landing. See generally Nat'l Human Genome Project Research Inst., <http://www.genome.gov/> (last visited Sept. 22, 2012) (providing information about HGP).

[FN15]. Harris, *supra* note 12.

[FN16]. Much of this background discussion is drawn from Malinowski, *supra* note 10, at 1-16, and Hughes, Jakimo & Malinowski, *supra* note 6, at 383-445.

[FN17]. See Malinowski, *supra* note 10, at 2.

[FN18]. See generally Roger L. Geiger, *Research & Relevant Knowledge* (2004). "The two largest R&D efforts of the war were the Manhattan Project and the Radiation Laboratory at MIT." *Id.* at 7; see also Galama & Hosek, *supra* note 13. According to one recent report on the state of U.S. investment in science relative to other nations:

Although China, India and South Korea are starting to account for a significant portion of the world's science and technology activities, and are showing rapid growth, they still account for a very small share of patents, science publications and citations. The United States, meanwhile, continues to invest in science and technology infrastructure, is creating significant employment in science and engineering, and benefits from the immigration of foreign-born science and engineering students and workers.

Id. See also Statistics, Nat'l Sci. Found., <http://www.nsf.gov/statistics/> (last visited Sept. 22, 2012) (providing detailed, timely data on R&D expenditures).

[FN19]. See Malinowski, *supra* note 10, at 2-9.

[FN20]. See generally Eisenhower, *supra* note 9. See also Smith, *supra* note 9, at 3-4.

[FN21]. Geiger, *supra* note 18, at 6-7 ("Given the absolute priority of the war effort, the usual academic tasks of universities were largely displaced for the duration."). "The basic relationship between the federal government and universities for conducting wartime research was governed by contracts negotiated according to the principle of no-loss and no gain. Universities were reimbursed for the direct costs they incurred and also given some allowance for overhead." *Id.* at 6. Thus the precedent for "administrative overhead" that later became commonplace with federal grant funding for bench research was established.

[FN22]. See generally *id.*

[FN23]. See *id.* at 19-20.

[FN24]. Vannevar Bush, U.S. Office of Sci. Research & Dev., *Science: The Endless Frontier* (1945), available at <http://www.nsf.gov/od/lpa/nsf50/vbush1945.htm>.

[FN25]. Richard A. Epstein, *Overdose: How Excessive Government Regulation Stifles Pharmaceutical Innovation* 3 (2006).

[FN26]. See *id.* at 5.

[FN27]. See Smith, *supra* note 9, at 3-10.

[FN28]. See generally U.S. Gov't Accountability Office, GAO-98-126, *Technology Transfer: Administration of the Bayh-Dole Act by Research Universities* (1998) [hereinafter GAO Technology Transfer]. There were some strong exceptions, however. The most notable was the Massachusetts Institute of Technology ("MIT"), which has a legacy of valuing application in its science curriculum. See *id.*

[FN29]. See generally *id.*

[FN30]. See generally *id.*

[FN31]. See generally *id.*

[FN32]. See Geiger, *supra* note 18, at xvi; see also James Stuart, *The Academic-Industrial Complex: A Warning to Universities*, 75 U. Colo. L. Rev. 1011, 1032-35 (2004).

[FN33]. See Barton Beebe, *Law's Empire and the Final Frontier: Legalizing the Future in the Early Corpus Juris Spatialis*, 108 Yale L.J. 1737, 1744-45 (1999). As explained by Beebe:

The immediate effect of the Sputnik Crisis in America was a call for total mobilization, for "blood, sweat and tears," in pursuit of scientific and technological superiority. This call extended to the nation's educational system, to its industrial base, to its commodity culture, and, of course, to its methods of governance. Ever prudent, Eisenhower refused to be carried away by the panic. In his 1958 State of the Union Address, he declared that the Soviet Union had begun to wage "total cold war," but proposed only modest reforms. It was left to the Kennedy and Johnson Administrations, to the New Frontier and the Great Society, to wage total cold war in return.

Id. at 1745.

[FN34]. See Geiger, *supra* note 18, at xv.

[FN35]. *Id.*

[FN36]. *Id.*

[FN37]. *Id.*

[FN38]. U.S. Dep't of Labor, Household Data Annual Averages: Employment Status of the Civilian Noninstitutional Population, 1941 to Date (2012), available at <http://www.bls.gov/cps/cpsaat01.pdf>.

[FN39]. See Alan S. Blinder, The Anatomy of Double-Digit Inflation in the 1970s, in *Inflation: Causes and Effects* 261, 270-71 (1982), available at http://www.nber.org/chapters/c11462.pdf?new_window=1.

[FN40]. See Michael S. Sherry, In the Shadow of War: The United States Since the 1930s 329-31 (1995); Hughes, Jakimo & Malinowski, *supra* note 6, at 392.

[FN41]. Hughes, Jakimo & Malinowski, *supra* note 6, at 392.

[FN42]. *Id.* at 393; see also Geiger, *supra* note 18, at 311.

[FN43]. See GAO Technology Transfer, *supra* note 28, at 2-3 (“At the time, fewer than 5 percent of the 28,000 patents being held by federal agencies had been licensed, compared with 25 percent to 30 percent of the small number of federal patents for which the government had allowed companies to retain title to the invention.”); Chester G. Moore, Killing the Bayh-Dole Act's Golden Goose, 8 *Tul. J. Tech. & Intell. Prop.* 151, 153-54 (2006); see also Stuart, *supra* note 32, at 1033-34 (“Whereas the major principle in the decades after World War II was that technology owned by the government was for ‘everyone's benefit,’ supporters of the [Bayh-Dole Act] claimed that this policy effectively rendered government-owned technology for ‘nobody's benefit.’ It simply gathered dust in government repositories.”).

[FN44]. Bayh-Dole University and Small Business Patent Procedures Act of 1980, Pub. L. No. 96-517, 94 Stat. 3019 (codified as amended at 35 U.S.C. §§ 200-211 (2006)).

[FN45]. Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, 94 Stat. 2311 (codified as amended at 15 U.S.C. §§ 3701-3715 (2006)). This legislation grants government researchers some of the opportunities allotted to academic researchers under Bayh-Dole. *Id.*

[FN46]. Hughes, Jakimo & Malinowski, *supra* note 6, at 393-94 (internal quotation marks omitted) (citing GAO Technology Transfer, *supra* note 28, at 3). See generally Matthew Herder, Asking for Money Back-Chilling Commercialization or Recouping Public Trust in the Context of Stem Cell Research?, 9 *Colum. Sci. & Tech. L. Rev.* 203 (2008) (providing a detailed discussion of the proposed recoupment provisions and associated testimony). As explained by the NIH, the collective goal of these Acts “is to promote economic development, enhance U.S. competitiveness, and benefit the public by encouraging the commercialization of technologies that would otherwise not be developed into products due to lack of incentives.” Office of Tech. Transfer, Nat'l Insts. of Health, NIH Response to the Conference Report Request for a Plan to Ensure Taxpayer Interests Are Protected (2001) [hereinafter NIH Report], available

at http://www.ott.nih.gov/policy/policy_protect_text.html. Later, Congress added to these Acts with enactment of the Federal Technology Transfer Act of 1986, which authorizes federal agencies to enter into cooperative research and development agreements (“CRADA”) with non-federal partners to conduct research. See Federal Technology Transfer Act of 1986, 15 U.S.C. § 3710(a) (2006). In 1987, the Department of Commerce issued regulations, codified in 37 C.F.R. 401 (2012), to fully implement Bayh-Dole. For a clear summary of the requirements set forth in these regulations, see GAO Technology Transfer, *supra* note 28, at 5.

[FN47]. See Michael J. Malinowski & Radhika Rao, Legal Limitations on Genetic Research and the Commercialization of Its Results, 54 Am. J. Comp. L. 45, 45 (2006). The GAO evaluated the impact of technology transfer in a report issued in 1998 and the NIH did the same in 2001. See generally GAO Technology Transfer, *supra* note 28; NIH Report, *supra* note 46. Reports also have been done by consulting groups such as the Boston Consulting Group, and on the national and state levels. See Bos. Consulting Grp., *The Pharmaceutical Industry into Its Second Century: From Serendipity to Strategy* (1999), available at <http://www.pharmaceuticalonline.com/doc.mvc/The-Pharmaceutical-Industry-Into-Its-Second-C-0004>. State reports can be accessed through the state affiliates' links on the Biotechnology Industry Organization website at <http://www.bio.org>.

[FN48]. Editorial, *Innovation's Golden Goose*, *Economist*, Dec. 12, 2002, available at <http://www.economist.com/node/1476653>.

[FN49]. Geiger, *supra* note 18, at xvi.

[FN50]. Hughes, Jakimo & Malinowski, *supra* note 6, at 398; see also Angell, *supra* note 12, at 101 (“With the 1980 Bayh-Dole legislation, the traditional boundaries between academia and industry were blurred. Academic medical centers now saw themselves as ‘partners’ of the pharmaceutical industry in common endeavors-and junior partners, at that.”).

[FN51]. Lorelei Ritchie de Larena, *The Price of Progress: Are Universities Adding to the Cost?*, 43 *Hous. L. Rev.* 1373, 1375 (2007). For another evaluation of Bayh-Dole, see generally David C. Mowery et al., *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer Before and After the Bayh-Dole Act* (2004).

[FN52]. See, e.g., EuropaBio, <http://www.europabio.org> (last visited Aug. 11, 2012). EuropaBio is a Europe-based international trade organization that blankets over numerous individual country affiliates. *Id.*

[FN53]. Angell, *supra* note 12, at 114.

[FN54]. Steve Morgan et al., *The Cost of Drug Development: A Systematic Review*, 100 *Health Pol'y* 4, 14-16 (2011). Industry estimates that new drugs cost over \$1 billion and take more than 15 years to produce, with an extraordinary failure rate. *Id.* The underlying data is proprietary. Industry voluntarily

provides data to the Tufts Center for the Study of Drug Development and funds studies to process it, which is where the drug cost numbers are drawn from. See Tufts Ctr. for the Study of Drug Dev., <http://www.csdd.tufts.edu> (last visited Sept. 22, 2012).

[FN55]. Harris, *supra* note 12.

[FN56]. NIH Budget, Nat'l Insts. of Health, <http://www.nih.gov/about/budget.htm#note> (last visited Aug. 12, 2012).

[FN57]. The NIH Almanac, Nat'l Insts. of Health, <http://www.nih.gov/about/almanac/appropriations/index.htm> (last visited Aug. 12, 2012).

[FN58]. See Harris, *supra* note 12; see also NIH Budget, *supra* note 56.

[FN59]. See Human Genome Project Information, *supra* note 14; NIH Budget, *supra* note 56.

[FN60]. See Harris, *supra* note 12.

[FN61]. See Drug Approval Reports, U.S. Food & Drug Admin., <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.MonthlyApprovalsAll> (last visited Sept. 23, 2012).

[FN62]. Epstein, *supra* note 25, at 7.

[FN63]. Harris, *supra* note 12; see also Asher Mullard, 2010 FDA Drug Approvals, 10 *Nature Revs. Drug Discovery* 82, 82-85 (2011). The FDA's Center for Drug Evaluation and Research approved twenty-one new drugs in 2010: fifteen new molecular entities and six new biologics. The agency approved twenty-five in 2009 and twenty-four in 2008. *Id.* at 82; see also Harris, *supra* (“The new effort comes as many large drug makers, unable to find enough new drugs, are paring back research.”).

[FN64]. Jeffrey P. Braff et al., Patient-Tailored Medicine, Part One: The Impact of Race and Genetics on Medicine, 2 *J. Health & Life Sci. L.* 1, 16 (2008); see also Bd. on Health Care Servs., Inst. of Med., Preventing Medication Errors 5 (Philip Aspden et al. eds., 2007) (estimating a minimum of 1.5 million preventable medication errors per year in hospitals, nursing homes, and ambulatory care settings in the United States). See generally Inst. of Med., *The Future of Drug Safety: Action Steps for Congress* (2006), available at http://www.iom.edu/~media/Files/Report%20Files/2006/The-Future-of-Drug-Safety/futureofdrugsafety_reportbrief.pdf. Efficacy failure may be as high as 60% of prescriptions. Barbara J. Evans, Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era, 85 *Notre Dame L. Rev.* 419, 498 (2010). In the words of some thoughtful observers: “To some extent, clinical medicine always has been tailored to the patient in that each physician-patient relationship is unique, and each clinical encounter represents the physician's attempt to provide the optimal care to the patient in the examining room, the emergency room, the hospital bed, and the

intensive care unit.” Wylie Burke & Bruce M. Psaty, *Personalized Medicine in the Era of Genomics*, 298 *JAMA* 1682, 1682-84 (2007). However, as much attention is placed on the patient, adverse drug reactions have been accepted as part of the practice of medicine. David Classen, *Medication Safety: Moving from Illusion to Reality*, 289 *JAMA* 1154, 1154-56 (2003); see also Braff, *supra*, at 9. Negative outcomes may result both from errors in prescribing and dispensing, and from individuals' adverse reactions to the drugs themselves. See Petra A. Th rmann, *Prescribing Errors Resulting in Adverse Drug Events: How Can They Be Prevented?*, 5 *Expert Opinion on Drug Safety* 489, 489-93 (2006). The varied rates of metabolizing drugs among individuals probably is a significant factor. See Kathryn A. Phillips et al., *Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions*, 286 *JAMA* 2270, 2270-79 (2001).

[FN65]. Braff et al., *supra* note 64, at 28 (addressing a need to shift single subject from delivery of care to drug development).

[FN66]. Barkur Sriram Shastry, *Pharmacogenetics and the Concept of Individualized Medicine*, 6 *Pharmacogenomics J.* 16, 16-21 (2006).

[FN67]. Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies*, 279 *JAMA* 1200, 1204 (1998).

[FN68]. John Carey, *Medical Guesswork*, *Bloomberg BusinessWeek*, May 28, 2006, available at <http://www.businessweek.com/stories/2006-05-28/medical-guesswork> (reporting on the movement for evidence-based medicine). See generally Angell, *supra* note 12. An important study released in 1995, confirming studies based upon autopsies done before, indicated that 15% of all diagnoses are inaccurate, and the advent of genomics has made the practice of medicine more complicated since then. See Jerome Groopman, *How Doctors Think* 24 (2007). As explained by Dr. Groopman:

Clinical algorithms can be useful for run-of-the-mill diagnosis and treatment-distinguishing strep throat from viral pharyngitis, for example. But they quickly fall apart when a doctor needs to think outside their boxes, when symptoms are vague, or multiple and confusing, or when test results are inexact. In such cases-the kinds of cases where we most need a discerning doctor-algorithms discourage physicians from thinking independently and creatively. Instead of expanding a doctor's thinking, they can constrain it.

....

... Medicine is, at its core, an uncertain science.

Id. at 5, 7.

[FN69]. The culmination of congressional concern was enactment of the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C. (2006)). “Public confidence in FDA fell from 80% in the 1970s to 61% in 2000; 56% in 2004;

and 36% in 2006.” Evans, *supra* note 64, at 431; see also Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 *Admin. L. Rev.* 431, 442-43 (2008) (citing Bill Hubbard and Steven Grossman, *Presentation to the FDA Alumni Association, Harris Poll Survey* (Apr. 11, 2007)).

[FN70]. See generally U.S. Gov't Accountability Office, *GAO-06-402, Drug Safety: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Processes* (2006) [hereinafter *GAO FDA Report*], available at <http://www.gao.gov/new.items/d06402.pdf>; Inst. of Med., *The Future of Drug Safety: Action Steps for Congress* (2006) [hereinafter *IOM Report*], available at http://www.iom.edu/~media/Files/Report%20Files/2006/The-Future-of-Drug-Safety/futureofdrugsafety_reportbrief.ashx. Both the GAO and IOM have criticized the FDA's performance regulating new drugs in the marketplace and emphasized the need to make the clinical research data submitted for market approval transparent to the public. See generally *GAO FDA Report*, *supra*; *IOM Report*, *supra*. Neither Congress nor the FDA have addressed the possibility that the drop off in innovative new drug approvals and poor performance of many on the market are an indication that the integrity of the entire forthcoming generation of biopharmaceuticals has been jeopardized by law and policy that comprehensively integrated academia and industry without shoring up the public nature of science. See generally Malinowski, *supra* note 10. During the span of the career of a single academic researcher now in her late 50s, norms have shifted from independence from industry, collegiality, disclosure and sharing of materials and information, quick and unfettered publication, and broad dissemination of information that invited meaningful scrutiny and rigorous peer review to strong technology transfer administration within academic research institutions, reward based upon commercialization, no communication without executed confidentiality and disclosure agreements and provisional patent applications, no publication without sponsor preapproval, and no sharing of materials without executed material transfer agreements. See generally *id.*

[FN71]. See W. John Thomas, *The Vioxx Story: Would It Have Ended Differently in the European Union?*, 32 *Am. J.L. & Med.* 365, 370-73, 379-80 (2006).

[FN72]. *GAO FDA Report*, *supra* note 70, at 10; see also Evans, *supra* note 64, at 428-43; Michael J. Malinowski, *Doctors, Patients, and Pills-A System Popping Under Too Much Physician Discretion? A Law-Policy Prescription to Make Drug Approval More Meaningful in the Delivery of Health Care*, 33 *Cardozo L. Rev.* 1085, 1111 (2012).

[FN73]. Bengt D. Furberg & Curt D. Furberg, *Evaluating Clinical Research* 8 (2d ed. 2007).

[FN74]. Michael J. Malinowski & Grant G. Gautreaux, *Drug Development-Stuck in a State of Puberty?: Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability*, 56 *St. Louis U. L.J.* 363, 394 (2012); see also Harlan Krumholz, *What Have We Learnt from Vioxx?*, 334 *Brit. Med. J.* 120, 120-23 (2007) (“Rofecoxib (Vioxx) was introduced by Merck in 1999 as an effective, safer alternative to non-steroidal anti-inflammatory drugs for the treatment of pain associated with osteoarthritis. It was subsequently found to increase the risk of cardiovascular disease and removed from the worldwide market.”). “Academic medicine, industry, medical journals, and

government agencies need to come together to define a set of principles by which we can restore faith in collaborations on new treatments that can improve patient care.” Id. at 122; see also Miho Nagano, Big Pharma Looks for a Fix, Bay Ledger News Zone (Sept. 26, 2008), http://www.blz.com/news/2008/09/27/Pharma_Looks_9571.html (the Vioxx controversy has inspired drug companies to undertake more toxicology studies); Thomas, *supra* note 71, at 365.

[FN75]. Gina Kolata, When Drugs Cause Problems They Are Supposed to Prevent, N.Y. Times, Oct. 17, 2010, at A18, available at <http://www.nytimes.com/2010/10/17/health/policy/17drug.html>.

[FN76]. Id.

[FN77]. Id. Avandia triggered an expansive U.S. Senate Finance Committee inquiry and bipartisan report highly critical of both GlaxoSmithKline (“GSK”) and the FDA. See Staff of S. Comm. on Fin., Report on Glaxosmithkline and the Diabetes Drug Avandia, S. Doc. No. 111-41, at 2 (2d Sess. 2010). The drug was introduced to the market in 1999 and prescribed to hundreds of thousands of patients annually to treat type-2 diabetes. Id. at 1-2. It caused 83,000 heart attacks between 1999 and 2007 according to the FDA’s own estimates. Id. at 4. GSK researchers identified a link to serious heart disease in 2003, 2005, and 2006; the FDA issued a warning in 2007; two of the FDA’s top officials in the Office of Surveillance and Epidemiology recommended a full market recall; and internal FDA reports indicated that switching Avandia patients to an alternative drug could prevent about 500 heart attacks and 300 cases of heart failure each month. See generally id. The Senate reported that executives at Glaxo “attempted to intimidate independent physicians, focused on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that a competing drug might reduce cardiovascular risk.” Id. at 1. GSK responded by defending Avandia. Id. GSK is undertaking another round of clinical trials, but those will not be completed until 2020. Gardiner Harris, Research Ties Diabetes Drug to Heart Woes, N.Y. Times, Feb. 19, 2010, at A1, available at <http://www.nytimes.com/2010/02/20/health/policy/20avandia.html?pagewanted=all>. There is a movement to reform the FDA to grant officials in the Office of Surveillance and Epidemiology independent decision making power on par with those who approve drugs. See Alyah Khan, Recent Avandia Report Sparks Concerns Over Internal FDA Power Struggle, FDA Wk., Feb. 26, 2010, available at 2010 WLNR 4078219. This suggestion was made years earlier, including in the Institute of Medicine’s 2006 Report on the FDA and in the law literature. See IOM Report, *supra* note 70, at 3; Thomas, *supra* note 71, at 380.

[FN78]. Kolata, *supra* note 75; see also Malinowski & Gautreaux, *supra* note 74, at 394-95.

[FN79]. Harris, *supra* note 12 (“The cost of bringing a single drug to market can exceed \$1 billion, according to some estimates, and drug companies have typically spent twice as much on marketing as on research, a business model that is increasingly suspect.”).

[FN80]. Ryan Savitz, CROs: The ‘Big Pharma Effect,’ Seeking Alpha (Aug. 28, 2008), <http://seekingalpha.com/article/93031-cros-the-big-pharma-effect>.

[FN81]. Boozang et al., *supra* note 11, at 6.

[FN82]. See generally Thomas, *supra* note 71, at 371-80; Epstein, *supra* note 25. For example, Professor Richard Epstein promotes relaxation of the overall regulation of an industry going through a difficult time:

What is needed now is a regeneration of moral and intellectual awareness that with this overdose of regulation on all fronts we are headed rapidly down the wrong path. If some greater understanding is acquired, then perhaps there will be some way, apart from political bashing, to nurse a besieged industry back to health so that it can resume its efforts to supply new and valuable products for the next generation.

Id. at 239. Dr. David Gratzer agrees:

Part of the problem is the FDA's excessive regulations. Since 1964, the total time required for drug development, from synthesis of the molecule to marketing approval, has more than doubled, now topping fifteen years. It's not just the incredible delay that's problematic: according to the Tufts Center for the Study of Drug Development, pharmaceutical companies spend almost \$900 million to bring a drug to market. Thirty years ago, the cost was a small fraction, \$138 million (adjusted for inflation). The bureaucratic hurdles, in other words, have been set too high. FDA caution is undermining our ability to make new drugs and save lives.

David Gratzer, *The Cure: How Capitalism Can Save American Health Care* 152 (2006).

[FN83]. See Angell, *supra* note 12, at xv-xvi. See generally Jamie L. Aldes, *The FDA Clinical Trial Process: Effectuating Change in the Regulatory Framework Governing Clinical Trials to Account for the Historical Shift from "Traditional" to "New" Phase I Trials*, 18 *Health Matrix* 463, 463 (2008) ("The culture within the FDA [is] one where the pharmaceutical industry, which the FDA is supposed to regulate, is seen by the FDA as its client instead."); Malinowski & Gautreaux, *supra* note 74; Thomas, *supra* note 71, at 366-71. The criticism on public record is penetrating:

The lack of adequate regulation of the pharmaceutical industry by the FDA has led to many deaths and recalls of unsafe drugs, such as Vioxx, that the FDA had approved for public use [in 1999]. As Sen. Charles Grassley (R-Iowa) explained, "Consumers should not have to second-guess the safety of what's in their medicine cabinet." Unfortunately, many consumers suffer as a result of the current ineffective state of the FDA's regulatory framework governing the drug testing and approval process.

Malinowski & Gautreaux, *supra*, at 395 n.165.

[FN84]. See Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 356b (2006); see also Angell, *supra* note 12, at 257 ("Driven by its lust for profits, [the pharmaceutical industry] seems almost

bent on eventual self-destruction. Its current way of doing business is not sustainable.”). The Vioxx controversy did force the FDA to raise its level of scrutiny, including more toxicology studies, and drug sponsors now must comply with the Food and Drug Administration Amendments Act of 2007 (“FDAAA”). See generally Am. Coll. of Physicians, *Improving FDA Regulation of Prescription Drugs* (2009), available at http://www.acponline.org/advocacy/where_we_stand/policy/fda.pdf; Thomas, *supra* note 71, at 371-73. Nevertheless, the FDA's resources have not been augmented commensurate with the FDAAA and much more thorough examination of new drug applications is needed.

[FN85]. See Food and Drug Administration Modernization Act § 506B. Section 506B of FDAMA, the provision that promotes this presumption in favor of market approval, is accompanied by FDA enforcement authority under 21 U.S.C. § 356b (2006). See Food & Drug Admin., *Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997* 1 (2001), available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/991852GD1.pdf>. The purpose of Phase IV (on-the-market) studies is to probe lingering questions and to perfect clinical use. See Peter Barton Hutt et al., *Food and Drug Law* 734-38 (3d ed. 2007); see also Christopher D. Zalesky, *Considering Changes to CMS's National Coverage Decision Process: Applying Lessons Learned From FDA as a Regulator of Access to Healthcare Technology*, 57 *Food & Drug L.J.* 73, 86-88 (2002) (“PDUFA II [[, enacted in conjunction with FDAMA,] shifted the agency's focus from one based solely on protecting the public from unsafe and ineffective products, possibly at the cost of expediency, to one that must balance this interest in safety with an interest in providing patients with speedy access to new drugs.”); James L. Zelenay, *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 *Food & Drug L.J.* 261, 295 (2005).

[FN86]. See GAO FDA Report, *supra* note 70, at 24, 27-28. See generally IOM Report, *supra* note 70. More than 144 drugs have reached the market conditionally since 1992. See 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* 18 (2009) [hereinafter *GAO New Drug Safety*], available at <http://www.gao.gov/new.items/d09866.pdf>. According to the GAO, the FDA has allowed drugs to stay on the market even when follow-up studies showed they did not save lives. See *GAO New Drug Safety*, *supra*, at 33. Although more than one-third of these conditional studies are pending, the FDA never has pulled a drug from the market because of a failure to do required follow-up about actual benefits-even when the information is more than a decade overdue. See *FDA Poised to Recall Unproven Blood Pressure Drug*, *USA Today*, Aug. 16, 2010, http://www.usatoday.com/money/industries/health/2010-08-16-fda-unproven-drug_N.htm. For example, Shire Pharmaceuticals has failed to complete a study for ProAmatine, a medication for low blood pressure, for more than 13 years. See *id.* This failure is consistent with GAO and IOM declarations that the FDA's performance post-drug approval is substandard. See generally IOM Report, *supra*; *FDA Poised to Recall Unproven Blood Pressure Drug*, *supra*.

[FN87]. See generally Margaret Gilhooley, *Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, Preemption, and the Drug Reform Legislation*, 59 *S.C. L. Rev.* 347 (2008). It is routine to exclude

children and women from trials for drugs for conditions that afflict them—for example, asthma in children and heart disease in women. Robert Preidt, *Children Usually Excluded from Clinical Trials: Study*, MSN (Apr. 30, 2012), [http:// healthyliving.msn.com/diseases/asthma/children-usually-excluded-from-clinical-drug-trials-study-2](http://healthyliving.msn.com/diseases/asthma/children-usually-excluded-from-clinical-drug-trials-study-2); see also Carol S. Weisman & Sandra D. Cassard, *Health Consequences of Exclusion or Underrepresentation of Women in Clinical Studies (I)*, in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* Volume 2 35, 35 (1999).

[FN88]. Malinowski *supra* note 72, at 1101.

[FN89]. *Id.* at 1104-05.

[FN90]. Angell, *supra* note 12, at 98. New drugs are not compared head-to-head with those already on the market. *Id.* “Maybe many new drugs are actually worse than old ones. Unless we test the new against the old, head to head, there is simply no way to know.” *Id.* at 99. New drugs should be compared with others on the market that treat the same conditions. *Id.* at 240. “If there is really doubt about whether a standard treatment is effective, the FDA should require that clinical trials of new treatments have three comparison groups—new drug, old drug, and placebo.” *Id.* at 241. If compared with existing treatments, few me-too drugs would be approved. *Id.* at 241-42. The standard should be changed to ask: “Does this drug add something of value to our ability to treat this condition? Not, ‘Can I create a big market for this drug.’” *Id.* at 242.

[FN91]. See *Clinical Trial Facts & Figures for Health Professionals*, CISCRP, http://www.ciscrp.org/professional/facts_graphs.html (last visited July 6, 2012).

[FN92]. Angell, *supra* note 12, at 95. Marcia Angell argues vigorously about the bias in industry surveys and the failure to compare new drugs with the ones already on pharmacy shelves. *Id.* at 107-09.

[FN93]. *Id.* at 95. Dr. Angell questions the reliance on industry trials, and she does so with troubling empirical data. For example, she reports that “[o]ne recent survey showed that authors of industry-funded studies were more than five times as likely to recommend the company drug as authors of studies funded by nonprofit organizations—regardless of the actual results.” *Id.* at 107. She also states that “often, bias is built into the study design, as is the case with placebo-controlled clinical trials. Almost inevitably new me-too drugs seem to be effective.” *Id.*

[FN94]. See generally Malinowski & Gautreaux, *supra* note 74 (questioning domestic reliance on the group design model for clinical research); Michael J. Malinowski & Grant G. Gautreaux, *All That Is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development*, 45 *Cornell Int'l L.J.* 185, 201-03 (2012) (proposing a change in the international standard to complement group design with single subject methodology).

[FN95]. Angell, *supra* note 12, at 100-01. Academic medical centers have been largely pushed out of clinical research, with industry favoring CROs. *Id.* “Whereas in 1990, about 80 percent of industry-

sponsored trials were done at academic institutions, within a decade that share had dropped to less than 40 percent.” Id. at 101. Medical schools and teaching hospitals, facing revenue reductions due to shrinking patient care reimbursements and cuts in medical education support, are forced to compete with CROs-and pressured to become more accommodating to pharmaceutical sponsors of trials. Id.

[FN96]. According to Dr. Angell:

[I]nstead of relying on academic centers to test their drugs, drug companies turned to the new for-profit research industry that grew up to serve them. . . . [T]hese companies contract with private doctors to collect data on patients in their offices according to company instructions. The doctors are not themselves trained researchers, so they simply do what they are told-or risk losing their lucrative deals with the contractors. The contract research organizations, in turn, answer only to big pharma. That means the drug companies have nearly total control over these trials.

Id. at 100-01. Dr. Angell summarizes key problems with clinical research. Id. at 239. She makes a strong argument to check the presence of the biopharmaceutical sectors in medical education:

[D]rug companies pour money into medical schools and teaching hospitals, they support most continuing medical education, and they subsidize professional meetings. Wherever clinicians are educated, big pharma is there to help. There is no question that it influences educational content. The result is that doctors not only receive biased information but learn a very drug-intensive style of medicine. They come to believe that there is a drug for everything and that new drugs (of which they have many free samples) are always better than old ones.

Id. at 250.

[FN97]. Id. at 100.

[FN98]. Id. at 102 (“One recent survey showed that two-thirds of academic medical centers hold equity in start-up companies that sponsor some of their research.”).

[FN99]. Id. at 104. Senior NIH scientists-among the highest paid government employees-also have financial entanglements. Id. According to 2003 investigative reporting by David Willman published in the Los Angeles Times, “NIH scientists (who are among the highest paid employees in the government) routinely supplement their income by accepting large consulting fees and stock options from drug companies that have dealings with the institutes.” Id. A 1995 change in NIH law under then-Director Harold Varmus eliminated the restrictions against this outside income, which senior scientists are not required to disclose: “[A]s of 2003, more than 94 percent of the agency's 2,259 top scientists did not have to reveal their outside consulting income.” Id. at 104-05.

[FN100]. Id. at 102-03. “[D]rug companies now design clinical trials to be carried out by researchers who are little more than hired hands-whether the trials are in academic centers or in physicians' offices.

Sponsoring companies keep the data, and in multicenter trials, they may not even let the researchers themselves see all of it. They also analyze and interpret the results, and decide what, if anything, should be published.” *Id.* at 112. “Often, in fact, they publish positive results more than once, in slightly different forms in different journals. The FDA has no control over this selective publishing. The practice leads doctors to believe that drugs are much better than they are, and the public comes to share this belief, on the basis of media reports. There is a general inflation in the notion of the good that drugs can do (and a deflation in concern about side effects).” *Id.* Dr. Angell offers examples, including the antidepressants Zoloft and Paxil and liberal prescribing of estrogen and progesterone hormone replacement for decades. *Id.* at 112-13. A NIH study suggested that the combination of hormone therapy would actually increase-rather than prevent-heart disease. *Id.* at 113.

[FN101]. *Id.* at 105-06 (quoting Editorial, *Subverting U.S. Health*, L.A. Times, Dec. 7, 2003, at M4, available at 2003 WLNR 15122262). “The pharmaceutical industry is everywhere in Washington, all but writing the Medicare prescription drug bill, fielding more lobbyists than there are members of Congress, flinging gifts and trips at doctors and trying to prevent double-blind drug trials that pit one drug against another, instead of against a placebo.” Editorial, *supra*.

[FN102]. See Janet Woodcock et al., *Development of Novel Combination Therapies*, 364 *New Eng. J. Med.* 985, 986-87 (2011).

[FN103]. See Rachel Behrman Sherman et al., *New FDA Regulation to Improve Safety Reporting in Clinical Trials*, 365 *New Eng. J. Med.* 3, 3 (2011).

[FN104]. Angell, *supra* note 12, at 244-46. Dr. Angell has proposed the creation of an institute to oversee the clinical testing of drugs. *Id.* In Dr. Angell's words:

To ensure that clinical trials serve a genuine medical need and to see that they are properly designed, conducted, and reported, I propose that an Institute for Prescription Drug Trials be established within the National Institutes of Health (NIH) to administer clinical trials of prescription drugs.

. . . .

. . . This is not a perfect process, and there may be better alternatives, but the point is that an independent, public agency should administer all clinical trials to ensure that they are properly conducted-both scientifically and ethically.

Id. at 245-46 (emphasis omitted).

[FN105]. See Harris, *supra* note 12.

[FN106]. Harris, *supra* note 12; see also FAQ: Proposed National Center for Advancing Translational Sciences, NIH Feedback, [http:// feedback.nih.gov/index.php/faq-ncats/](http://feedback.nih.gov/index.php/faq-ncats/) (lasted updated Jan. 11, 2011)

[[hereinafter NCATS Proposal].

[FN107]. NCATS Proposal, *supra* note 106. According to the NIH:

This proposed Center is envisioned to be a tremendous resource for the entire translational science community. It would develop and offer innovative services and expertise in moving promising products through the development pipeline, as well as develop novel approaches to therapeutics development, stimulate new avenues for basic scientific discovery, and complement the strengths of existing NIH research activities.

Id.

[FN108]. See NCATS Proposal, *supra* note 106; Harris, *supra* note 12; Gerald Weissmann, Is Drug Development Too Slow? NIH to the Rescue!, 25 *FASEB J.* 1119, 1119-20, 1122 (2011). Dr. Collins, working with an advisory committee and Congress, is proposing to establish the center by reorganizing NIH-integrating translational research programs, drawing from the National Human Genome Research Institute, the National Center for Research Resources, and the NIH Director's Common Fund. NCATS Proposal, *supra*.

[FN109]. Woodcock et al., *supra* note 102, at 985.

[FN110]. Mullard, *supra* note 63, at 83 (“Increasingly, however, firms are moving towards specialty-care and orphan-disease markets.”). Patient outcomes are becoming an increasing point of focus for reimbursement. *Id.*

[FN111]. See discussion *supra* Part III.

[FN112]. Angell, *supra* note 12, at 256 (“[Prescription drug companies] are not just squeaking by, as industry apologists imply, but in recent years are making three to six times the profits earned by other Fortune 500 companies.”). In 2002, U.S. drug companies reaped more total profits than the profits of all other Fortune 500 companies combined. *Id.*

[FN113]. See generally Boozang et al., *supra* note 11. Government researchers stepped away from directly engaging in human clinical research, resulting in the present dependency on industry to conduct the clinical trials necessary to develop innovative new drugs—as documented in a White Paper issued in the fall of 2009 by Seton Hall Law School. *Id.*

[FN114]. Best Pharmaceuticals for Children Act of 2002, 42 U.S.C. § 284m (2006).

[FN115]. *Id.*

[FN116]. Nat'l Insts. of Health, Research, NCATS, <http://www.ncats.nih.gov/research/research.html> (last

visited Aug. 12, 2012); Nat'l Insts. of Health, Molecular Libraries Probe Production Center, NCATS, <http://www.ncats.nih.gov/research/reengineering/ncgc/mlp/mlppc.html> (last visited Aug. 12, 2012). Although it does not do so often, NIH has conducted clinical trials with great success. For example, the National Heart, Lung, and Blood Institute conducted a mammoth trial of the treatment of high blood pressure (hypertension) with over 42,000 subjects at more than 600 clinics. Angell, *supra* note 12, at 95-96. It was the largest clinical trial ever done for the treatment of high blood pressure. *Id.* The trial concluded that diuretics were just as effective at lowering blood pressure and better at preventing heart disease and strokes than newer drug alternatives. *Id.* at 96. Moreover, while diuretics were priced at \$37 a year in 2002, a generic angiotensin-converting enzyme inhibitor was priced at \$230 and the marquee market competitor Norvasc was priced at \$715. *Id.* at 97.

[FN117]. Epstein, *supra* note 25, at 12.

[FN118]. Henry I. Miller, Correspondence, FDA Not NIH Can Speed New Drugs, 472 *Nature* 169, 169 (2011).

[FN119]. Epstein, *supra* note 25, at 239-40.

[FN120]. Human Genome Project Information, *supra* note 14.