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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

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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

Michael J. Malinowski*

ABSTRACT

This article challenges the scope of physician discretion to engage in off-label use of prescription drugs. The discretion to prescribe dimensions beyond the clinical research that puts new drugs on pharmacy shelves has been shaped by two historic influences: a legacy of physician paternalism, solidarity, autonomy, and self-determination that predates the contemporary commercialization of medicine by more than half a century, and regulatory necessity due to the limits of science and innate crudeness of pharmaceuticals prior to the genomics revolution (drug development and delivery based upon genetic expression). Although both factors have changed immensely, the standard for drug approval has lingered. This article proposes that doctor discretion to prescribe off label must be modified and the regulatory standard for new drug approvals raised given the proliferation of adverse events, drug ineffectiveness, the need to make choices among treatment options under time pressures, the increasing complexity of biopharmaceuticals, health care cost pressures, and the vulnerability of patients—seekers of health care, not research subjects protected under the scrutiny of regulations to protect human subjects. The article concludes that, although some physician discretion to prescribe off label still is necessary, law-policy reforms to shift more of the drug discovery process from the clinical care of patients to clinical research in drug development are long overdue. Proposals to accomplish this, drawn from recent legislation and ongoing health care reform, include heightening the regulatory standards for new drug approvals and drug reimbursement.

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1960-1970¹

The United States Senate held hearings in January 1970 to address widespread adverse events, including strokes and deaths, associated with the birth control pill—which the Food and Drug Administration (FDA) had approved for market use nearly a decade before. At the time, the pill was being taken by approximately six million women annually, with consumption rising rapidly.² Although the issue was serious health risks to women and for a medication taken solely by women, only men were allowed to testify. As explained by Dr. Philip Ball,

It was an enormous room, full of people. Well, I simply told them that I was in

¹ The following was transcribed by the author from *The Pill* (PBS Home Video, 2003).

² This testimony was inspired in part by BARBARA SEAMAN, *THE DOCTORS' CASE AGAINST THE PILL* (1969). In spite of this experience with the pill, estrogen was aggressively prescribed to postmenopausal women without attention to cancer risks until the late 1990s. As explained by Dr. Groopman, The growth in prescriptions of estrogen for postmenopausal women can be traced to a bestseller published in the 1960s, *Feminine Forever*, by Dr. Robert A. Wilson. It turned out that a drug company that made estrogen had paid Dr. Wilson to write the book. JEROME GROOPMAN, *HOW DOCTORS THINK* 210 (2008).

practice, and that I was suddenly afflicted by all these young women taking the pill that had all these problems Mind you, the dose of the pill in those days was ten times what it is now. It was a huge blockbuster pill they used as a sledgehammer to drive a small nail. You know, it was an unnecessary dose.

A group of young feminists who themselves had taken the pill attended the hearings. According to advocate Alice Wolfson, a leader within the group,

We began to hear researcher after researcher, male after male, start saying things about the pill, and then one doctor I believe said “Fertilizer is to weed what estrogen is to cancer” It just all seemed so outrageous to us that we were not given any information when we were given the pill. It was literally handed out like candy.

A protest erupted, which captured more media attention than the hearings it disrupted. As a result, hormone levels in the pill were slashed, the occurrence of side effects greatly diminished, and the FDA required manufacturers to include information in every package listing potential risks. The most significant change was that women demanded a new kind of relationship with their doctors. As reflected upon by Dr. Richard Hausknecht:

The bad patient, she’d walk in pregnant with the husband and “Here are my demands”—that was a phenomena of the 70s. “I won’t have this, I will have that, and I won’t have this,” and they got this from the same medical political activist that I was. And it was terrifying to me to hear myself give a lecture to a lay group about why they should not let doctors do all these things to them, and those same damn patients came back to my office and made those demands of me, and it used to upset the hell out of me.

I. INTRODUCTION

The roles of physician and patient have changed immensely in the U.S. over the decades since the 1970 U.S. Senate hearings on the pill. The “silent world of doctor and patient”³ at the time of the hearings still lingers to some extent today,⁴ but medicine has been commercialized and the medical profession has lost a considerable amount of its autonomy, solidarity, and self-determination. Factors that have drained the sovereignty of the medical profession include increasing dependence on outside institutions (hospitals and government regulators, for example) in conjunction with the progressive sophistication of the practice of medicine, the commercialization of medicine, the rise of consumer-driven medicine in an internet age, aggressive direct-to-consumer marketing by the biopharmaceutical sectors which encourages patients to make drug demands on their

³ See generally Jay Katz : JAY KATZ, THE SILENT WORLD OF DOCTOR AND PATIENT (1984) (discussing a “millennia of Hypocratic paternalism”).

⁴ See Susan M. Wolf, *Doctor and Patient: An Unfinished Revolution*, 6 YALE J. HEALTH POL’Y, L. & Ethics 485, 485-500 (2006). Cf. GROOPMAN, *supra* note 2.

physicians, legislation that enables patients to check and control the flow of their medical information, and public and political challenges to the entire health care system with ongoing, sweeping federal and state reforms underway.⁵ Similarly, in many ways today's FDA is fundamentally different from the agency that put the pill on the market in 1960. The FDA's very mission has changed from policing safety and efficacy with a presumption in favor of caution. Since modernization of the FDA in 1997, the agency is under a mandate to achieve review efficiency through increased responsiveness to industry during the drug approval process,⁶ and there is a presumption to put drugs on the market on a wait-and-see basis—which is what happened with Vioxx.⁷ More than 900 FDA reviewers are salaried through the collection of user fees from the sponsors of the new drugs they regulate.⁸

In spite of these changes, the fundamental law-policy governing drug approval and delivery remains vested in the past. Specifically, this article questions broad physician discretion to prescribe pharmaceuticals off label. Too much reliance is placed on the medical profession to develop meaningful understanding of pharmaceuticals *after* they are on the market, one patient at a time, especially in an age of unprecedented science precision through advances in human genetics.⁹ The discussion centers on the

⁵ See generally *Symposium—Patient-Centered Law and Ethics*, 45 WAKE FOREST 1429 (2010); PRICEWATERHOUSECOOPERS, HEALTH REFORM: PROSPERING IN A POST-REFORM WORLD (2010) [hereinafter “PWC REPORT”]. DAVID GRATZER, THE CURE, at xvi (“Between 2000 and 2006, health costs have soared and health insurance premiums have roughly doubled. It’s not simply employers who feel the pinch. Consider a family’s perspective. . . . In fact, since the early 1970s, health spending per capita has increased fivefold, adjusting for inflation.”). The employer cost of health insurance has been soaring:

Employers during the Bush years paid handsomely for labor. In fact, employers’ costs for employing a typical, median worker jumped from \$19.85 per hour in 200 to \$25.67 in 2006. That’s a raise of more than \$5 per hour, or 25%.

Yet the average worker saw none of the money. Every dime—and then some—was gobbled up by the rising cost of employer provided health insurance

Look at this from the point of view of some typical American family. Married, two kids. Between 2000 and 2006, their pay has barely gone up at all. They’ve had a nice little tax cut from the Bush Administration, worth perhaps \$500. But they’re paying \$1,100 more per year in out-of-pocket health care costs.*Id.* at xvi, quoting DAVID FRUM, COMEBACK: CONSERVATISM THAT CAN WIN AGAIN (2009).

⁶ See 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, 74-75 (2002).

⁷ See generally W. John Thomas, *The Vioxx Story: Would it have Ended Differently in the European Union?*, 32 AM. J. L. & MED. 365 (2006) [hereinafter “Vioxx Story”]; MARCIA ANGELL, THE TRUTH ABOUT DRUG COMPANIES (2004).

⁸ See generally FDA, Prescription Drug User Fee Act (PDUFA), available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm> (last visited July 31, 2011); Dep. Health & Human Serv’s, Prescription Drug User Fee Rates for 2012, available at http://www.ofr.gov/OFRUpload/OFRData/2011-19332_PL.pdf (last visited July 31, 2011). See generally James L. Zelenay, Jr., *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 (2005).

⁹ As explained by one commentator,

Once a drug is approved, however, the FDA cannot control how physicians actually prescribe it. Physicians can prescribe any drug for any medical condition, even outside of the parameters of the label, for a so-called “off-label” use. Therefore, off-label use is the prescription of a

changed status of the medical profession and surrounding circumstances since the off-label norms were established last century.

The article begins with discussion of how the broad discretion to prescribe dimensions beyond the clinical research that puts new drugs on pharmacy shelves is the product of two historic influences. The first is a legacy of paternalism and tremendous physician autonomy that predates the contemporary commercialization of medicine, and the second is regulatory necessity due to the limits of science and innate crudeness of pharmaceuticals prior to the genomics revolution (drug development and delivery based upon genetic expression). Although these norms have changed immensely over the last several decades, the standard for drug approval remains vested in the past.

Part III addresses the state of drug delivery and development today—a problem of over delivery of prescription pharmaceuticals off-label by physicians that is no longer supported in our health care system. The article discusses the history of the authority of the AMA over health care and the pharmaceutical marketplace, and how the AMA’s role has changed, making its broad discretion to prescribe off label antiquated and questionable. Excessive off-label prescribing detracts from patient care directly and through its impact on drug development.

The article concludes that doctor discretion to prescribe off label must be modified to improve human health and drug development. Law-policy proposals are put forth to shift drug discovery from doctor offices to the clinical research that puts them on pharmacy shelves.

II. THE BACKSTORY TO CONTEMPORARY OFF-LABEL USE: AUTONOMY, PATERNALISM, AND THE LIMITS OF DRUG DEVELOPMENT

Expansive physician discretion to prescribe beyond the clinical research that puts new drugs on the market is reflective of two historic influences, each of which is addressed below. The first is a legacy of physician paternalism, self-determination, and autonomy that predates the contemporary commercialization of medicine. The second is regulatory necessity attributable to the limits of science and innate crudeness of most pharmaceuticals prior to the genomics revolution.

A. PHYSICIAN AUTONOMY, SELF-DETERMINATION, AND PATERNALISM

The medical profession’s response to the television series *Marcus Welby, MD*, which aired from 1968 to 1976 and was the biggest hit in ABC’s history at the time,¹⁰ exemplifies the autonomy, solidarity, and PATERNALISM the AMA enjoyed prior to

pharmaceutical product at a dose and/or for a condition that the FDA has either not reviewed or not approved. Off-label uses of drugs are commonplace. For example, most drugs historically were tested and approved for use in adults; therefore, physicians who wanted to treat similar indications in pediatric patients by definition had to use the drugs off-label.

Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225 n.114 (2011).

¹⁰ JOSEPH TUROW, PLAYING DOCTOR: TELEVISION, STORYTELLING, & MEDICAL POWER 143 (2010).

changes that began in the 1970s. The show portrayed Dr. Marcus Welby, the consummate family doctor, and his young assistant, Dr. Steven Kiley, played by James Brolin. The two were responsive to PATIENTS as individuals, and they worked to humanize medicine against a system of formality and specialization that promoted too many uncaring doctors.

The physician community responded loudly and defensively to the television series. They complained “that millions of Americans were becoming resentful of their physicians for not living up to the image of the wise and caring physician” and that the show was stirring up medical malpractice actions.¹¹ The debate that ensued, set in the age of television with heavy national viewership, was the first time that the physician establishment engaged in a large-scale public debate over whether *patient positive* fictional depictions of doctors detracted from their status, and it generated extensive coverage—including articles in *The New York Times Magazine* and *McCall’s* that received much attention and fueled the controversy.¹² Robert Young, the actor who played Dr. Welby, took on a group of family physicians personally at a large national convention:

Robert Young went even so far as to chide physicians publicly for not living up to his Welby image. At one convention of family physicians, for example, a doctor said to Young, “You’re getting us all into hot water. Our patients keep telling us we’re not as nice to them as Doctor Welby is to his patients.” Young didn’t mince words. “Maybe you’re not,” he said.¹³

Public and professional reactions to *Marcus Welby, MD* and the Senate hearings and controversy over the pill are two illustrations of how the 1970s was a period of transition for the doctor-patient relationship. Paul Starr, winner of the Pulitzer Prize for general nonfiction for the *Social Transformation of American Medicine*, recognized the same in 1984—years prior to proliferation of the managed care movement that he predicted,¹⁴ and the commercialization and national health care reform eras that have followed:¹⁵

When I began work in 1974, it was widely thought that medical schools, planners, and administrators were emerging as the chief counterweight to private physicians. Government seemed to be assuming a major, perhaps dominant role in the organization of medical care. Decisions that had formally been private and professional were becoming public and political. Eight years later this is no longer clearly the direction of change, but neither is the status quo ante being restored. Private corporations are gaining a more powerful position in American medicine; if leading members of the Reagan administration have their way, the future may well belong to corporate medicine. . . . Precisely because of what is now taking place, it has become more necessary to understand medicine as a

¹¹ *Id.* at 170.

¹² *Id.*. Henry Enrich, *The Nice Men Cometh*, MCCALL’S MAG.23 (May 1972).

¹³ TUROW, PLAYING DOCTOR, *supra* note 10, at 143.

¹⁴ See generally Michael J. Malinowski, *Capitation, Advances in Medical Technology, and a New Era in Medical Ethics*, 22 AM. J.L. & MED. 331 (1996).

¹⁵ PAUL STARR, *THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE* ix-x (1982).

business as well as a cultural phenomenon—and perhaps most important, to understand the relation between the two.

The current level of discretion physicians have over drug delivery, the focus of this article, is rooted in the medical profession’s autonomous, self-determining past. An element of physician authority is innate: The delivery of patient care is necessarily individualized,¹⁶ and “The sick are ordinarily not the best judge of their own needs, nor are those who are emotionally close to them.”¹⁷ However, the U.S. medical profession’s story throughout the 20th century is exceptional: “Hardly anywhere have doctors been as successful as American physicians in resisting national insurance and maintaining a predominantly private and voluntary financing system.”¹⁸ The U.S. physician community has been at least as effective creating direct returns for itself:¹⁹

The profession has been able to turn its authority into social privilege, economic power, and political influence. . . . Until recently, it has exercised dominant control over the markets and organizations in medicine that affect its interests. . . . At all these levels, from individual relations to the state, the pattern has been one of professional sovereignty.

A major factor unique to the U.S. is the political influence of the bond between medicine and science—which cannot be underestimated in such a forward-looking nation that has and continues to invest so much government and private funding in biomedical research.²⁰ Specifically, the medical profession has enjoyed “an especially persuasive claim to authority. Unlike the law and the clergy, it enjoys close bonds with modern science, and at least for most of the last century, scientific knowledge has held a privileged status in the hierarchy of belief.”²¹ In fact, the rise of the influence and autonomy of the American medical profession correlates with the organization and formalization of medical education at the turn of the 20th century—starting with the introduction of a four-year graduate program with a clinical teaching hospital component by Johns Hopkins University in 1893.²² Harvard University soon followed, other universities were inspired to do the same, and states funded programs to increase their

¹⁶ See 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*, __ ST. LOUIS L. REV. __, __ (forthcoming 2011) [hereinafter “*Drug Puberty?*”].

¹⁷ STARR, *supra* note 15, at 5.

¹⁸ *Id.* at 6.

¹⁹ *Id.* at 5.

²⁰ PhRMA, 2010 REPORT IV (2011). Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at Part III.A.; 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*, 20 HOFSTRA L. REV. 101, 386-401 (2009). See general Malinowski, *Discourse: A Law-Policy Proposal to Promote the Public Nature of Science in an Era of Academia-Industry Integration*, in BIENNIAL REVIEW OF LAW, SCIENCE AND TECHNOLOGY: SCIENCE GOVERNANCE, FREEDOM OF RESEARCH, AND PLURALIST DEMOCRACY (2009).

²¹ STARR, *supra* note 15, at 4. Malinowski, *Discourse*, *supra* note 20, at II.A.

²² STARR, *supra* note 15, at 115-116. Johns Hopkins University took the lead in U.S. medical education by opening its medical school in 1893—a 4-year program and requirement that all applications enter with college degrees. *Id.* See generally ALAN M. CHESNEY, THE JOHNS HOPKINS HOSPITAL AND THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, VOL. 1, EARLY YEARS, 1867-1893 (1943).

populations' access to quality medical care through education and teaching hospitals.²³ A population of physicians with graduate medical degree credentials was established, and they called for and helped to implement and enforce licensing requirements and other standards for the practice of medicine.²⁴ "In the twentieth century, not only did physicians become a powerful, prestigious, and wealthy profession, but they succeeded in shaping the basic organization and financial structure of American medicine."²⁵

The medical profession managed to hold control over the practice of medicine and block outside interests, government and corporate, from 1900 until 1930.²⁶ Solo private practitioners, the majority of physicians during this time, wanted to keep their relationships with their patients unimpeded.²⁷ However, the Great Depression launched the gradual infusion of outside organizations and entities into the private practice of medicine—namely hospitals, government regulators, insurers, pharmaceutical companies, and other corporate interests.²⁸ The paradox the American medical profession has faced over its status is that its authority has risen in conjunction with therapeutic competence enabled through science and technology, but the infusion of science and technology has raised the need for capital investment and dependence on organizations such as hospitals, pharmaceutical companies and, more recently, commercial health care networks.²⁹ "In 2009, America's pharmaceutical research and biotechnology companies continued to make the world's largest investment in pharmaceutical R&D, holding steady with \$65.3 billion spent on R&D, including \$45.8 billion by PhRMA members alone."³⁰

Hospitals were the first organizations to meaningfully crack the medical profession's control over the practice of medicine. The Johns Hopkins University model of combining medical education with clinical hospital practice and joining science research and hospital care—precedent for the teaching hospital staple we know today—lifted the status of hospitals immensely.³¹ The resulting science advances affirmed the union: hospitals were lifted from sanitariums where the dying were ostracized to institutions delivering care and the potential to heal.³² The bridge between the medical profession and hospitals, once erected, became national. Private medical schools, funded through philanthropic donations and high tuition, were expensive and offered limited access.³³ Therefore, as the capabilities of medicine expanded, state land grant

²³ STARR, *supra* note 15, at 115-116. *See generally* MARTIN KAUFMAN, AMERICAN MEDICAL EDUCATION: THE FORMATIVE YEARS, 1765-1910 (1976)

²⁴ *See* STARR, *supra* note 15, at 102-112, 123. *See generally* *State Requirements of Preliminary Education*, 79 JAMA 658 (Aug. 19, 1922).

²⁵ STARR, *supra* note 15, at 7-8.

²⁶ *Id.* at 198-232.

²⁷ *Id.*

²⁸ *Id.* at 270-279.

²⁹ *Id.* at 16.

³⁰ PhRMA, 2010 PROFILE iv (2011).

³¹ STARR, *supra* note 15, at 112-116.

³² *Id.* at 150-152.

³³ Hughes, Jakimo, & Malinowski, *Biomedical Research*, *supra* note 20, at 390-391; Jed Scully, *The Virtual Professorship: Intellectual Property Ownership of Academic Work in a Digital Era*, 35 MCGEORGE L. REV. 227, 241-42 (2004).

universities financed their own medical schools and teaching hospitals to meet their populations' demand for doctors and health care needs.³⁴

Insurers were the second category of organizations outside of the physician community to establish a meaningful foothold of influence over the practice of medicine. The Great Depression limited the ability of people to see and pay for doctor services, which raised the medical profession's responsiveness to insurance.³⁵ However, the major occurrence was the labor shortage during World War II. In 1942, the War Labor Board, which prohibited private employers from paying salaries above those offered by competitors engaged in the war effort, determined that fringe benefits up to five percent of base wages would not be considered inflationary.³⁶ Group hospital plans grew from enrollment of seven million subscribers to twenty-six million and, after the war, the popularity of employee health plans rose considerably—especially among large employers.³⁷ The organized labor and union movement during 1945-1959, promoted under the National Labor Relations Act of 1935, raised demand for employer-provided health insurance coverage, and the Internal Revenue Code accommodated by making the cost of health insurance a deduction for employers and a non-taxed benefit for employees.³⁸ The limits of health care relative to today made health care affordable, and appealing during an era in which employees often were loyal and remained employed by

³⁴ Hughes, Jakimo, & Malinowski, *Biomedical Research*, *supra* note 20, at 390-391.

³⁵ STARR, *supra* note 15, at 232-279.

³⁶ *Id.* at 311. A testament to the organization and strength of the AMA was the 1940 antitrust conviction against it in 1940 for conspiring against an early HMO. *See* United States v. Am. Med. Ass'n (AMA), 110 F.2d 703 (D.C. Cir. 1940), *cert denied*, 110 F.2d 703 (1940). *See generally* Sherman Antitrust Act, Act of July 2, 1890, ch. 647, 26 Stat. 209 (codified as amended at 15 U.S.C. §§ 1-7 (2008)). *See also* Amer. Med. Assoc. v. United States, 130 F.2d 233 (D.C. Cir. 1942), *aff'd*, 317 U.S. 519 (1943) (ruling that the practice of medicine is trade or commerce within the meaning of the federal antitrust laws); Amer. Med. Assoc. v. Fed Trade Com., 638 F.2d 443(2nd Cir. 1980), *aff'd by an equally divided court*, 455 U.S. 676 (1982). The courts clarified in the 1970s and 1980s that the medical profession is susceptible to anti-competition laws. *See e.g.*, Goldfarb v. Virginia State Bar, 421 U.S. 773 (1975) (eliminating the learned professions exemption to the federal antitrust laws); Arizona v. Maricopa County Med. Soc'y, 457 U.S. 332, 343-57 (1982) (holding that the maximum fee agreements of a state medical society, as price-fixing agreements, are per se unlawful under § 1 of the Sherman Act). Decades later but still on the eve of the full sweep of managed care and the commercialization of medicine, a federal court found that the AMA violated federal antitrust laws by conspiring to eliminate the chiropractic profession. *Wilk v. Am. Med. Ass'n*, 895 F.2d 352, 360 (7th Cir. 1990). However, overall, judicial decisions and federal policy have limited the role of antitrust laws in the reorganization of the health care sector. *See generally* Thomas L. Greaney, *Whither Antitrust? The Uncertain Future of Competition Law in Health Care*, 21 HEALTH AFFAIRS 185 (2000). The medical profession has attempted to limit its exposure to antitrust liability. *See* Clark C. Havighurst, *The Doctors' Trust: Self-Regulation and the Law*, 2 HEALTH AFFAIRS 64 (1983); Carl F. Ameringer, *Federal Antitrust Policy and Physician Discontent: Defining Moments in the Struggle for Congressional Relief*, 27 J. HEALTH POL. & L. 543 (2002). *See also* Sara Rosenbaum, *The Impact of United States Law on Medicine as a Profession*, 289 JAMA 1546, 1552-55 (2003).

³⁷ During this time, it was common for employees to work for a single employer for the entire duration of their career, which was an added incentive for employers to keep them healthy. *Healthcare Crisis: Who's at Risk?* (2000) (PBS video)

³⁸ National Labor Relations Act of 1935 ("Wagner Act"), Pub.L. 74-198, 49 Stat. 449, codified as amended at 29 U.S.C. § 151-169). STARR, *supra* note 15, at 310. Employer-provided health insurance continues to be a significant health care tax subsidy that often is overlooked in discussion of U.S. health care costs.

the same company for their entire careers.³⁹ The employer-based system was reinforced during the Cold War as the desirable alternative to socialized medicine.⁴⁰ The organization of private insurance benefited physicians. They were able to assume a gatekeeper role, meaning that insurers and patients placed dependence on them for reimbursement decision making, and the existence of insurance added assurance of payment.⁴¹ During this time, physicians were able to hold onto control over institutions and government by organizing professionally.⁴²

As a complement to the employer-based insurance system, the U.S. government enacted the Medicare and Medicaid programs under the Social Security Act in 1965.⁴³ President Lyndon B. Johnson was able to get the programs approved because their scope was limited to patching holes in the system by covering those unable to work—the elderly and disabled—with a methodology of moving federal funds through existing health care infrastructure.⁴⁴ Physicians and hospitals welcomed the influx of additional insured patients under the programs, and covering the elderly and disabled took pressure off of families and had innate popularity during a time of intense social, cultural, political, and economic change.⁴⁵

The federal government made another major move into the practice of medicine after 1962 through the addition of an efficacy requirement for FDA approval of new pharmaceuticals.⁴⁶ The thalidomide controversy was a catalyst for this elevation of the approval standard.⁴⁷ However, the law was written to be consistent with the established assurance that the FDA would not interfere with the practice of medicine—meaning physician discretion over clinical use of approved pharmaceuticals would remain respected.⁴⁸ As acknowledged by Professor Evans, “During the twentieth century, FDA pursued a policy of not regulating physicians. This was embodied in the agency’s permissive policy on off-label use.”⁴⁹

³⁹ Who’s at Risk?, *supra* note 37. See Evans, *Seven Pillars*, *infra* note 46, at 460.

⁴⁰ President Truman’s proposal for a national plan was rejected, but President Johnson credited him in the context of passage of the Medicare and Medicaid plans. See Who’s at Risk?

⁴¹ STARR, *supra* note 15, at 28.

⁴² *Id.*

⁴³ *Id.* at 369. Who’s at Risk?, *supra* note 37.

⁴⁴ Who’s at Risk?, *supra* note 37.

⁴⁵ ECOCOMIC EVENTS, IDEAS, AND POLICIES: THE 1960S AND AFTER (Eds. George L. Perry & James Tobin, 2000).

⁴⁶ Drug Amendments of 1962, Pub. L. No. 87-781, 102, 76 Stat. at 781-82 (amendment to 21 U.S.C. 355(d) to make lack of substantial evidence of efficacy a ground for denial of drug applications). The agency did not begin requiring all drug manufacturers to submit new drug applications until 1962. Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic ACT Enters the Genomics Era*, 85 NOTRE DAME L. REV. 419, 423 (2010).

⁴⁷ PETER BARTON HUTT, RICHARD A. MERRILL, & LEWIS A. GROSSMAN, FOOD AND DRUG LAW14 (3rd ed. 2007); JAMES T. O’REILLY, 1 FOOD & DRUG. ADMIN. § 13:2 (2011).

⁴⁸ See *infra* notes 49, 95-98 and the accompanying text. See also Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at n.235 and in the accompanying text (quoting former FDA Commissioner Kessler regarding FDAMA).

⁴⁹ See Evans, *Pillars*, *supra* note 46, at 509; *infra* note 98 and accompanying text. The House Report that accompanied FDAMA, enacted in 1997, expressly states that “FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-

The AMA had welcomed establishment of the predecessor of the FDA, the Bureau of Chemistry, in 1908-1909 to further its cause of capturing control over the flow of medical information, including information about pharmaceuticals.⁵⁰ The higher standard for drug approval augmented dependence upon physicians for clinical research and use of prescription pharmaceuticals. Drug makers worked even closer with the medical profession to expand their market presence, and that relationship has continued and strengthened.⁵¹

As illustrated by the U.S. experience with the pill,⁵² the 1970s marked the beginning of decades of escalating involvement in the practice of medicine by institutions outside of the physician community. In an environment of strong social reform movements, from college sit-ins to riots with fatalities, liberal critics of the U.S. health care system drove for more state intervention, which in turn augmented the involvement of employers, the insurance industry, and the federal government.⁵³ From the 1970s to the present, a health care rights movement has questioned the medical profession about informed consent,⁵⁴ other human subject protections,⁵⁵ patient involvement in therapeutic decision making,⁵⁶ the rights of patients to refuse treatment,⁵⁷ the right of

label uses of approved drugs is not within the jurisdiction of the FDA.” H.R.Rep. No. 105-310, at 60 (1997).

⁵⁰ The roots of today’s FDA date back to the Pure Food and Drug Act of 1906, though that law addressed only the most egregious fake drugs. See O’REILLY, *supra* note 47, at § 3:3 (*The Food and Drug Administration: A Brief History*); STARR, *supra* note 15, at 131. The predecessor of today’s FDA, the Bureau of Chemistry, was funded in 1909 with a budget of just \$685,460. STARR, *supra* note 15, at 129. The AMA’s efforts between 1900 and 1910 were threefold:

First, and perhaps most important, muckraking journalists and other Progressives joined physicians in a crusade for regulation of patent medicines as part of a more general assault on deceptive business practices. Second, as a result of its growing membership, the AMA finally acquired the financial resources to create its own regulatory apparatus and to mount a major effort against the nostrum makers [drugs with undisclosed ingredients]. And, third, the drug makers were forced to recognize that they depended increasingly on doctors to market their drugs because of the public’s increased reliance on professional opinion in decisions about medication.

Id. In 1905, the AMA closed its journal to patent medicine advertisements and established a Council on Pharmacy and Chemistry to set drug standards and evaluate them. *Id.*

⁵¹ See generally HUTT, MERRILL, & GROSSMAN, *supra* note 47. See *infra* note 112 and accompanying text (physician and pharmaceutical interests joined forces to challenge off-label marketing provisions of FDAMA).

⁵² See *supra* notes 1-2 and accompanying text.

⁵³ STARR, *supra* note 15, at 388.

⁵⁴ National Commission for the Protection of Human Subjects, established by the National Research Act of 1974 (Pub. L. 93-348), addressed the controversy and issued the Belmont Report in 1979, available at http://science.education.nih.gov/supplements/nih9/bioethics/guide/teacher/Mod5_Belmont.pdf, which makes voluntary, informed consent (“respect for persons”) its cornerstone tenet.

⁵⁵ See the Common Rule, 45 C.F.R. Part 46; FDA 21 CFR Parts 50, 56 (FDA human subject protections). For more information about the protection of human subjects, visit the Internet site of the Office for Human Research Protections (OHRP), <http://www.hhs.gov/ohrp/> (last visited Aug. 1, 2011).

⁵⁶ See generally KATZ, *supra* note 3; Wolf, *supra* note 4.

⁵⁷ See *Cruzon v. Dir.*, Missouri Dept. of Health, 497 U.S. 261 (1990); *In re Quinlan*, 70 N.J. 10, 355 A.2d 647 (NJ 1976)..

patients to see medical records,⁵⁸ freedom from genetic discrimination,⁵⁹ DNA ownership,⁶⁰ and other issues, culminating a call for comprehensive national health care reform.⁶¹

The medical profession also fractured internally, with fissures apparent even in the 1960s—especially between academic medicine and private practice, as the voice of the former grew in strength and influence.⁶² The profession and the delivery of care had exploded in size from 1950-1970 to become one of the U.S.’s largest industries.⁶³ During these two decades, the medical workforce more than tripled in size—from 1.2 to 3.9 million individuals—and national health care expenditure increased more than fivefold, from \$12.7 billion (4.5 percent of GNP in 1950) to \$71.6 billion (7.3 percent of GNP).⁶⁴ This growth promoted professional organizations on the state and regional levels and specialty-centered professional organizations—all of which made it more difficult for the AMA to address controversial issues and for the physician community to speak with a single voice.⁶⁵

By the 1980s, insurers, employers, and patients became frustrated with rising health care costs under a fee-for-service system that invited physicians to perform procedures and conduct tests well beyond patients’ actual health care needs, and to engage in all out fraud and abuse.⁶⁶ A managed care movement swept through the nation, and the U.S. entered an era of intense commercialization of medicine.⁶⁷ In the early 1980s, Paul Starr recognized the movement and its future scope:

More recently, the system has begun to slip from [physician] control as power has moved away from the organized profession toward complexes of medical schools and hospitals, financing and regulatory agencies, health insurance companies

⁵⁸ Health Insurance Portability and Accountability Act (HIPAA) of 1996 (P.L.104-191) [HIPAA].

⁵⁹ Genetic Information Nondiscrimination Act (GINA) of 2008 (P.L. 110-233),

⁶⁰ *See, e.g.,* The Ass’n For Molecular Pathology v. U.S. Patent and Trademark Office, ___ F.3d ___ (C.A.Fed. (N.Y.),2011), *available at* 2011 WL 3211513. *But see generally* RICHARD A. EPSTEIN, *OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION* (2006).

⁶¹ *See generally* Patient Protection and Affordable Care Act (PPACA), Pub. L. 111-148, 124 Stat. 119 (to be codified as amended in scattered sections of the Internal Revenue Code, 26 U.S.C., and 42 U.S.C.). For details about the reform, *see generally* PWC REPORT, *supra* note 5.

⁶² STARR, *supra* note 15, at 335; *id.* at 378 (“As the institutional side of medicine expanded, the medical profession itself became more divided, especially between academic medicine and private practice. The cohesiveness of the profession, so vital to its past successes, was beginning, like so many other things in the 1960s, to come apart. New interests emerged inside medicine that began to overshadow the private practitioners. And as public dissatisfaction increased with rising costs, these new forces threatened to reduce the sovereignty that private doctors had long exercised over medical care.”).

⁶³ *Id.* at 335.

⁶⁴ *Id.*

⁶⁵ *See generally supra* note 36 and accompanying text.

⁶⁶ *See generally* Michael J. Malinowski, *Capitation, Advances in Medical Technology, and the Advent of a New Era in Medical Ethics*, 22 *Am. J. L. & MED.* 335, 335-360 (1996 symposium), *reprinted in* TAKING SIDES: CLASHING VIEWS ON CONTROVERSIAL BIOETHICAL ISSUES (Carol Levine ed., 7th ed., 1997).

⁶⁷ *Id.*

prepaid health plans, and health care chains, conglomerates, holding companies and other corporations.⁶⁸

Solo practitioners have been swallowed up by health care networks and the rest of the commercial establishment as predicted, and commercialization has weakened patient trust and helped to fuel consumer-driven medicine.⁶⁹ The AIDS epidemic and the advent of information technology in the 1980s-1990s inspired information exchange among patients, at times globally, and patient group organization and advocacy, which rages on.⁷⁰ Pervasive direct-to-consumer marketing and internet information on pharmaceuticals has inspired patients to demand rather than simply receive prescriptions from physicians and, due to the frequency of job and employer insurance carrier changes, patients are switching primary care physicians with tremendous frequency. The world of doctor and patient still is too silent, especially with time pressures imposed by the commercialization of medicine, but patients are much more vocal, inquisitive, and cautious.

The U.S. now has moved into a new era which underscores the need question law and policy shaped by norms based upon what was the practice of medicine. Governments, federal and state, are taking much more control over the practice of medicine—most notably through the Patient Protection and Affordable Care Act (PPACA).⁷¹ The Act, though supported by the AMA, has greatly fractured its members.⁷² Though PPACA is being challenged in federal courts and the national debt raised questions about financial feasibility, states have and are working on comprehensive reforms. Some states, such as Massachusetts, took action years ago.

B. DRUG TREATMENT: DISEASE SYMPTOMS, NOT CAUSES

Human health has improved immensely through the progress of drug development since the middle of the 20th century and largely due to pharmaceutical R&D.⁷³ As reported by the Centers for Disease Control and Prevention (“CDC”), “During the 20th century, life expectancy at birth among U.S. residents increased by 62%, from 47.3 years

⁶⁸ STARR, *supra* note 15, at 7-8. *Id.* at 369.

⁶⁹ *See generally* Symposium—Patient-Centered, *supra* note 5.

⁷⁰ *See generally* Malinowski, *Capitation*, *supra* note 66.

⁷¹ *See generally* Patient Protection and Affordable Care Act (PPACA), Pub. L. 111-148, 124 Stat. 119 (to be codified as amended in scattered sections of the Internal Revenue Code, 26 U.S.C., and 42 U.S.C.); PWC REPORT, *supra* note 5.

⁷² *AMA Fractured, Leftists on Top, Private Doctors Say* (June 20, 2011) (the AMA House of Delegates affirmed support in a vote of 326-165); Robert Lowes, *AMA Supports Latest Health Care Reform Legislation With Reservations*, MEDSCAPE TODAY NEWS (Mar. 19, 2010), available at <http://www.medscape.com/viewarticle/718909> (last viewed Mar. 9, 2011). Interestingly, the AMA ended up generally endorsing the Act though in most of the country there are few too few doctors to absorb the more than 40 million insured patients the Act calls for. This is a major concern in Louisiana with a disproportionately large poor and uninsured population and a preexisting shortage of physicians since being struck by hurricanes Rita and Katrina. Presentation by Catherine Kitchen, Director of Policy, Department of Health and Hospitals, Louisiana State University Law Center, Health Law Survey (Apr. 2011). A possible solution considered by some states is to grant authorities traditionally held only by licensed M.D.s to other health care professionals, thereby diluting the traditional hold of physicians significantly. *Id.*

⁷³ GRATZER, CURE, *supra* note 5, at 143. *See generally* STARR, *supra* note 15.

in 1900 to 76.8 in 2000, and unprecedented improvements in population health status were observed at every stage of life.”⁷⁴ Vaccines have made a profound impact on the prevention of disease: they now prevent and in some cases control (polio and measles, for example) an impressive portfolio of seriously debilitating and life-threatening diseases.⁷⁵ Advances in the treatment of disease have been equally impressive: “Think of antibiotics that stop infection; beta-blockers that reduce heart attack mortality by a third; antihypertensives that prevent heart attacks in the first place; and the chemo agents that helped Lance Armstrong.”⁷⁶ These accomplishments have enabled the pharmaceutical sector to remain the most profitable one in the U.S. for over half a century.⁷⁷ Moreover, for decades, the tendency of U.S. patients has been to believe in prescription medications as the means to overcome their afflictions, and the general public assimilates medicine closely with science—especially when grappling with a seriously debilitating illness.⁷⁸

Nevertheless, relative to the elevation of science standards over the last few decades through the genomics revolution, overall, 20th Century drug development was a crude undertaking.⁷⁹ Drug sponsors were not even required to obtain an official market approval for market access until 1962.⁸⁰ Congress directed the FDA to require evidence of efficacy as well as safety and to engage in risk-benefit decision making.⁸¹ Prior to the

⁷⁴ Centers for Disease Control and Prevention, Ten Great Public Health Achievements—United States, 2001-2010 (2011), available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm?s_cid=mm6019a5_w. For an excellent discussion of diminishing returns in drug development, see generally *Rising Expectations—And Diminishing Returns*, in EPSTEIN, OVERDOSE, *supra* note 60, at 3-25.

⁷⁵ See generally Centennial Video, Center for Biotechnology Evaluation and Research (2002) (made publicly available; on file with author). For identification of vaccine preventable diseases, see Centers for Disease Control and Prevention, Vaccines and Preventable Diseases, available at <http://www.cdc.gov/vaccines/vpd-vac/default.htm> (last visited June 12, 2011).

⁷⁶ GRATZER, CURE, *supra* note 5, at 143. See generally GROOPMAN, *supra* note 2.

⁷⁷ See generally ANGELL, TRUTH, *supra* note 7.

⁷⁸ GRATZER, CURE, *supra* note 5, at 143.

⁷⁹ *Symposium, Proceedings of “The Genomics Revolution? Science, Law, and Policy*, 66 LA. L. REV. 1-143 (2005). As observed by Professor Epstein, “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.” EPSTEIN, OVERDOSE, *supra* note 60, at 239. See *Rising Expectations—And Diminishing Returns*, in *id.* at 3-25.

⁸⁰ Evans, *Seven Pillars*, *supra* note 46, at 423: “It was after 1962 that ‘FDA became responsible for making benefit-risk decisions’ about drugs. Congress directed FDA, for the first time, to require ‘substantial evidence’ of efficacy as well as safety. FDA interpreted this language to require the familiar three-phase clinical trial process through which drugs now pass before FDA approval.” Drug Amendments of 1962 (Harris-Kefauver Act), Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in 21 U.S.C.). HUTT, MERRILL, & GROSSMAN, *supra* note 47, at 434-435. *Vioxx Story*, *supra* note 7, at 365. See generally See generally Jeffrey P. Braff, et al., *Patient-Tailored Medicine Part One: The Impact of Race and Genetics on Medicine*, 2 J. HEALTH & LIFE SCI. LAW 1 (2008); Jeffrey P. Braff, et al., *Patient-Tailored Medicine, Part Two: Personalized Medicine and the Legal Landscape*, 2 J. HEALTH & LIFE SCI. L. 1, 7 (2009). See also David Classen, *Medication Safety: Moving from Illusion to Reality*, 289 JAMA 1154, 1154-56 (2003). Harris Meyer, *Medicine: Costly Stamp of Approval*, L.A. TIMES, Jan. 18, 2010, at p. 3, available at 2010 WLNR 1055167. Sponsors have been required to demonstrate safety since 1938. *Id.*

⁸¹ See Drug Amendments of 1962, Pub. L. No. 87-781, section 102, 76 Stat. at 781-782. See also INST. OF MED., UNDERSTANDING THE BENEFITS AND RISKS OF PHARMACEUTICALS 48 (Leslie Pray rapporteur, 2007); Evans, *Seven Pillars*, *supra* note 46, at 423.

1990s, the medicinal treatment of all human ailments consisted of heavy reliance on a mere 1,200 commercial pharmaceuticals derived from 483 drug targets (compounds that serve as the basis for medicinal applications).⁸² “[D]rug discovery essentially was a linear process based upon screening and testing of thousands of chemicals and natural substances for potential therapeutic activity. Screening was time consuming and largely random because drug targets and drug functions were in most cases unknown.”⁸³

The traditional drug development process developed in the 20th century centers on taking away disease symptoms, not understanding and treating disease causes.⁸⁴ Compounds are introduced into living organisms for observation to discern their impact, potential medicinal utilities are ascertained, new drug candidates are developed and purified through the drug approval process to control toxicity and perfect dosage for at least one medicinal use.⁸⁵ The baseline standard for market approval is to outperform a placebo (a sugar pill, meaning essentially nothing) on efficacy, perhaps just by a percentage point or two, with a showing of tolerable safety in a defined population.⁸⁶ Pharmaceuticals approved by the FDA are introduced onto the market with the expectation that physicians will experiment further through off-label uses while practicing medicine on patients, and thereby identify additional clinical utilities.⁸⁷

Though drug development has shifted in the direction of genetic precision (understanding disease pathways and the importance of genetic expression),⁸⁸ the

⁸² Jürgen Drews, *Drug Discovery: A Historical Perspective*, 287 *SCIENCE* 1960, 1960-64 (2000) [hereinafter Drews]. Thomas Reiss, *Drug Discovery of the Future: The Implications of the Human Genome Project*, 19 *TRENDS BIOTECHNOLOGY* 496, 496-99 (Dec. 2001); Michael J. Malinowski, *Respecting, Rather than Reacting to, Race in Basic Biomedical Research: A Response to Professors Caulfield and Mwaria*, 45 *HOUS. L. REV.* 1489, 1492 (2009). A Drug target is “a molecular structure (chemically definable by at least a molecular mass) that will undergo a specific interaction with chemicals that we call drugs because they are administered to treat or diagnose a disease. The interaction has a connection with the clinical effect(s).” *Id.* (page nos. not available online). Peter Imming, Christian Sinning, & Achim Meyer, *Drugs, Their Targets, and the Nature and Number of Drug Targets*, 5 *Nature Reviews Drug Discovery* 821-824 (Oct. 2006) (page nos. not available online), available at <http://www.nature.com/nrd/journal/v5/n10/full/nrd2132.html> (last visited June 21, 2009). “This surprisingly low number of targets illustrates that the identification of clinically relevant and interesting targets was the primary bottleneck of the drug discovery process.” Braff, *Patient-Tailored One*, *supra* note 80, at 11.

⁸³ Braff, *Patient-Tailored One*, *supra* note 80, at 11, citing Press Release, Tufts Ctr. for the Study of Drug Dev., Backgrounder: How New Drugs Move Through the Development and Approval Process (Nov. 2001), available at csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4; and Jim Gilbert, Preston Henske & Ashish Singh, Rebuilding Big Pharma’s Business Model, 21 *BUS. & MED. REP.* 1 (Nov. 2003), available at www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf.

⁸⁴ Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at III.A.

⁸⁵ See HUTT, MERRILL, & GROSSMAN, *supra* note 47, at 467-834.

⁸⁶ 21 C.F.R. pts 301-369. See also *Vioxx Story*, *supra* note 7, at 365.

⁸⁷ See *Washington Legal Found. v. Friedman*, 13 F.Supp.2d 51, 56 (D.D.C.1998) *vacated in part on other grounds*, 202 F.3d 331 (D.C.Cir.2000) (observing that “off-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine”); Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at nn. 17-20 and accompanying text.

⁸⁸ See generally *infra* Part III.B; PERSONALIZED MEDICINE COALITION, *THE CASE FOR PERSONALIZED MEDICINE* 1, 4 (Nov. 2006), available at www.personalizedmedicinecoalition.org/communications/TheCaseforPersonalizedMedicine_11_13.pdf

regulatory standard for market approval of a drug candidate in the U.S. remains largely the same: elimination of symptoms, even if just marginally more effectively than a placebo, coupled with a showing that adverse events and other safety issues across the target disease population are tolerable given the benefits.⁸⁹ Industry sponsors hold broad discretion to tailor clinical research and to apply (or not) for approval of specific uses in applications for market access, which provides an incentive to limit the scope of applications for market access, get approval, and then exploit physician off label use through sponsorship of research and conferences and the distribution of medical journal publications.⁹⁰

III. TODAY'S DRUG DELIVERY OVERDOSE AND *UNDERDEVELOPMENT*

Life science and medicine have changed fundamentally since the days of *Marcus Welby, M.D.*⁹¹ The traditional approach to drug development—heavy reliance on physician-patient use, on and off-label, to develop meaningful understanding of pharmaceuticals—must be modified to address the realities of contemporary health care and biopharmaceutical R&D. As addressed below, from the perspectives of both delivery of care and drug development, the traditional approach simply is not working, and adhering to it is imposing an opportunity cost to human health as well as an economic cost to the biopharmaceutical sectors.

A. DRUG DELIVERY OVERDOSE

The medical profession supported the Pure Food and Drug Act of 1906 and expansion of federal regulation of prescription pharmaceuticals throughout much of the 20th Century.⁹² The Drug Act was consistent with the AMA's campaign against the sale

(last visited May 6, 2011); Braff, *Patient-Tailored One*, *supra* note 80, at 16-17. See also Evans, *Seven Pillars*, *supra* note 46, at Part IV.A (anticipated clinical care uptake of genetic screens).

⁸⁹ See 21 C.F.R. pts 301-369; A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION 126 (Kenneth R. Piña & Wayne L. Pines eds., 2d ed. 2002); Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at 54-55 and in the accompanying text. Cf. John, *Vioxx*; *supra* note 54; Braff, *Patient-Tailored One*, *supra* note 80, at 9 (“Nonetheless, not until the second half of the twentieth century has much attention been paid to drug safety and, even then, adverse drug reactions were considered part of the practice of medicine.”); David Classen, *Medication Safety: Moving from Illusion to Reality*, 289 JAMA 1154, 1154-56 (2003).

⁹⁰ Washington Legal Foundation v. Henney, 202 F.3d 331, 333 (C.A.D.C. 2000). Off-label use of pharmaceuticals is “generally accepted” in the medical community and commonly practiced. See Washington Legal Found. v. Friedman, 13 F.Supp.2d 51, 56 (D.D.C.1998) *vacated in part on other grounds*, 202 F.3d 331 (D.C.Cir.2000) (observing that “off-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine”); Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 349, 121 S.Ct. 1012, 1018, 148 L.Ed.2d 854 (2001).

⁹¹ TUROW, *PLAYING DOCTOR*, *supra* note 10, at 143.

⁹² STARR, *supra* note 15, at 128-134. The Biologics Control Act of 1902 arguably is the baseline for what has become the regulation of contemporary biopharmaceuticals and established the predecessor for the Center for Biologics Evaluation and Research (CBER) within the FDA. CBER, Centennial, *supra* note 75 (video documentary released by CBER). The 1901 deaths of 13 children from tetanus attributable to contaminated diphtheria antitoxin inspired the legislation. National Institutes of Health, *A Short History of the National Institutes of Health*, available at http://history.nih.gov/exhibits/history/docs/page_03.html (last visited June 27, 2011). For the expansion of regulatory authority over pharmaceuticals, see *infra* notes 46-47 and accompanying text.

of snake oils (fabricated medicines, often dangerous to human health), and creation of a market gatekeeper for prescription medicines gave the AMA much more control over the flow of medical information and created dependence on the physician community for clinical research and patient use of pharmaceuticals.⁹³ Enforcement was expanded during the 1960s to instill an application and approval process for all new drugs as a prerequisite for market access and to impose an efficacy standard.⁹⁴

Although the AMA welcomed a government gate keeper for the pharmaceutical market, it did so with the condition that the FDA would not interfere with the practice of medicine—meaning physician discretion over clinical use of approved pharmaceuticals would remain respected.⁹⁵ This caveat has been codified in law and reinforced over

⁹³ In 1905, the AMA closed its Journal to advertisements for medicines under patent protection and established a Council on Pharmacy and Chemistry to set standards for drugs, evaluate them, and ensure their utility—an effort by the AMA to directly control information over pharmaceuticals from their manufacturers. STARR, *supra* note *supra* note 15, at 129-131. The AMA even set up a laboratory that collaborated with the federal Bureau of Chemistry to test food and drug law products. *Id.* at 131. Enactment of the Pure Food and Drug Act in 1906 established a national base for what would become the FDA, though this legislation only addressed the most egregious drug fakes. The legislation was implemented by the federal Bureau of Chemistry, a predecessor to the FDA. The Bureau was renamed the Food, Drug, and Insecticide Administration in 1927, which was shortened to the Food and Drug Administration in 1930. JAMES T. O'REILLY, *A BRIEF HISTORY OF THE FOOD AND DRUG ADMINISTRATION*, ch. 3, nn. 18-19 (2011). The Division of Biologics Control was established in 1937, followed by what has become the core FDA legislation, the Food and Drug Cosmetic Act of 1938, 21 U.S.C. §§ 301-397, and the Public Health Services Act of 1944 (“PHSA”) of 1944, 42 U.S.C. § 262. The Food, Drug & Cosmetics (FD&C) act was passed in response to the 1937 deaths of 105 patients poisoned by the antibiotic Sulfanilamide formulated with diethylene glycol. See P.M. Wax, *Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act*, 6 ANN INTERN MED. 456-61 (Mar. 15, 1995). Subsequently, legislation was enacted to address medical devices: the Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511 (codified in scattered sections of 21 U.S.C. and 42 U.S.C.); and the hMedical Device Amendments of 1992, Pub. L. No. 102-300, 106 Stat. 239 (codified in scattered sections of 21 U.S.C.). Cross reference. Michael J. Malinowski, *Choosing the Genetic Makeup of Children: Our Eugenics Past—Present, and Future?*, 36 Conn. L. Rev. 125, 180 (2003). The AMA’s efforts between 1900 and 1910 were threefold:

First, and perhaps most important, muckraking journalists and other Progressives joined physicians in a crusade for regulation of patent medicines as part of a more general assault on deceptive business practices. Second, as a result of its growing membership, the AMA finally acquired the financial resources to create its own regulatory apparatus and to mount a major effort against the nostrum makers. And, third, the drug makers were forced to recognize that they depended increasingly on doctors to market their drugs because of the public’s increased reliance on professional opinion in decisions about medication.” 1905: AMA closed its journal to patent medicine advertisements and established a Council on Pharmacy and Chemistry to set drug standards and evaluate them.

STARR, *supra* note 15, 129.

⁹⁴ 1962 amendments to FDCA: Drug Amendments of 1962 (Harris-Kefauver Act), Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C.); S Re. No. 1744 at 2920-21. STARR, *supra* note 15, 131-133. Evans, *Pillars*, *supra* note 46, at 501.

⁹⁵ See generally Marc A. Rodwin, *Drug Advertising, Continuing Medical Education, and Physician Prescribing: A Historical Review and Reform Proposal*, 38 J. L. MED. & ETHICS 807, 807 (2010).

time,⁹⁶ including in conjunction with enactment of the Food and Drug Administration Modernization Act of 2007.⁹⁷ As explained by Professor Evans,⁹⁸

During the twentieth century, FDA pursued a policy of not regulating physicians. This was embodied in the agency's permissive policy on off-label use. This policy let physicians choose to disregard instructions and warnings in drug labeling. FDA took the position that "labeling is not intended either to preclude the physician from using his best judgment in the interest of his patient, or to impose liability if he does not follow the package insert." This policy made a certain amount of sense under the 1962 regulatory paradigm, which focused FDA's attention on average safety and efficacy. Unable to provide meaningful guidance about individual safety and efficacy, FDA left this determination to physicians.

The legacy of physician discretion over the use of pharmaceuticals continues. Once drugs reach the market, the medical community may exercise its broad discretion to use them off-label, and it does so aggressively.⁹⁹ Prescription uses without supportive clinical data are commonplace in all areas of medicine, but even more frequent in some medical areas such as oncology and pediatrics.¹⁰⁰ Pediatric data is insufficient, at times

⁹⁶ See 21 U.S.C. § 396 (2000) (medical device regulation); 42 U.S.C. § 1395 (2000) ("Nothing in [Medicare] shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided."); Legal Status of Approved Labeling for Prescription Drugs: Prescribing Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) (to be codified at 21 CFR pt. 130) ("[I]t is clear that Congress did not intend the [FDA] to regulate or interfere with the practice of medicine"); *FTC v. Simeon Mgmt. Corp.*, 391 F. Supp. 697, 706-07 (N.D. Cal. 1975), *aff'd*, 532 F.2d 708, 717 (9th Cir. 1976). See also Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at 108, 235, and in the accompanying text; Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 720, 731-2 (2005); Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 397-98 (2002) (off label use is particularly aggressive in some medical specialties, including oncology specialties).

⁹⁷ The House Report that accompanied FDAMA expressly states that "FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-label uses of approved drugs is not within the jurisdiction of the FDA." H.R.Rep. No. 105-310, at 60 (1997). As for legal challenges, in 2000 the Court of Appeals for the District of Columbia determined that Food and Drug Administration Modernization Act ("FDAMA") provisions addressing manufacturer promotion of off-label use imposed an undue burden on commercial free speech in violation of the First Amendment. See generally *Washington Legal Foundation v. Henney*, 202 F.3d 331 (C.A.D.C. 2000). At issue in the case were the FDA's and Congress' attempts to regulate two promotional strategies: manufacturer dissemination to physicians of independent medical and scientific publications concerning the off-label uses of their products (referred to as "enduring materials"), and manufacturer support for Continuing Medical Education (CME) programs for doctors that focus on off-label uses. See generally *id.*

⁹⁸ Evans, *Seven Pillars*, *supra* note 46, at 509 (internal citations omitted).

⁹⁹ Rodwin, *supra* note 95, at 807 ("Because of their medical knowledge, physicians are authorized to prescribe drugs even for uses unapproved by the FDA").

¹⁰⁰ See generally *id.* See also Eisenberg, *supra* note 96, at 731. "Off-label prescribing is very common in all areas of medicine. It is not uncommon for a drug to be prescribed more often off-label than on-label" Daniel B. Klein & Alexander Tabarrok, *Do Off-label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians' Argumentation for Initial Efficacy*, 67 AM. J. ECON. & SOC. 743 (2008) (internal citations omitted; page numbers not available online). According to these

wholly lacking, for two-thirds of prescription drugs.¹⁰¹ Even with extensive off-label use, children often are the last to receive innovative new drugs due to a dearth of clinical data.¹⁰² The FDA attempted to force pediatric studies, but it was sued successfully by a collaboration between the physician community and pharmaceutical sector.¹⁰³

Physician choice to use prescription medications to treat any health ailment regardless of the data submitted to the FDA for market approval was functional and to some extent necessary during much of the last century.¹⁰⁴ Throughout most of that time, the entire prescription drug arsenal to treat all human illness consisted of several hundred pharmaceuticals developed from a few hundred compounds,¹⁰⁵ and the limit of science capabilities restricted the scope of clinical research that was practicable.¹⁰⁶ Health care needs coupled with limited science understanding invited physician ingenuity in treating patients. The FDA itself was undeveloped in function and funded miserly given its responsibilities after the new drug application and efficacy standard requirements were introduced in the 1960s.¹⁰⁷ Also, there was healthy distance between the medical profession and pharmaceutical sector through the medical profession's independence and influence, patient deference to physician decision making, and the limited mass media reach of the drug industry. Pharmaceutical marketing was contained by the FDA as the agency evolved and exercised more authority in the 1970s, and prior to the first Prescription Drug User Fee Act (PDUFA) in 1992 and the Food and Drug Administration Modernization Act in 1997 (FDAMA).¹⁰⁸ PDUFA established a user fee system in which industry negotiated with Congress and the FDA and agreed to pay user fees for application review. FDAMA, negotiated in conjunction with PDUFA renewal, increased FDA transparency and accountability and expanded the FDA's mission to work with industry to increase efficiency and bring new drugs to market quicker—especially innovative new drugs for untreated or insufficiently treated life-threatening or seriously

authors, “Most cancer and AIDS patients are given drugs that are not FDA certified for the prescribed use. In a large number of fields, a majority of patients are prescribed at least one drug off-label.” *Id.*

¹⁰¹ “Indeed, 80 percent to 90 percent of pediatric patient regimens involve at least one off-label prescription.” Klein & Tabarok, *Off-label*, *supra* note 100, at 743. *See also* Kristal M. Wicks, *Exhausted or Unlicensed: Can Field-of-Use Restrictions in Biotech License Agreements Still Prevent Off-Label Use Promotion After Quanta Computer?*, 9 U. N.H. L. REV. 157, 163 (2010); Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at 236-251 and the accompanying text (addressing pediatric exclusivity).

¹⁰² *See* 63 Fed.Reg. at 66,632. *See* Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at 232.

¹⁰³ Association of American Physicians and Surgeons Inc., et al, v. United States Food and Drug Administration, 226 F.Supp.2d 204 (Oct. 17, 2002), 2002 WL 31323411 (D.D.C.); Hearings on Better Pharmaceuticals for Children Act at 4 (2002) (statement of Janet Heinrich, Director, Health Care-Public Health Issues). *See* Malinowski & Gautreaux, *Drug Puberty?*, at 241-241. Congress enacted legislation to create the means for the FDA to get desired pediatric studies done directly, regardless of industry support. *See infra* notes 212-218 and accompanying text.

¹⁰⁴ *Cf. Rising Expectations—And Diminishing Returns*, in EPSTEIN, OVERDOSE, *supra* note 60, at 3-25.

¹⁰⁵ *See supra* note 82 and accompanying text. The inventory of prescription pharmaceuticals used routinely did not reach 1,200 until the 1980s. The number of overall approvals is much higher, however. *See* Evans, *Seven Pillars*, *supra* note 46, at 428-429.

¹⁰⁶ STARR, *supra* note 15, at 135.

¹⁰⁷ The FDA did not even require new drug applications until 1962, following by a showing of efficacy. *See supra* notes 46, 80, 99 and the accompanying text.

¹⁰⁸ *See supra* notes 1-2 and the accompanying text.

life-debilitating conditions.¹⁰⁹ During the 1990s, industry joined forces with patient groups to support increases in government (NIH) funding of basic research and to demand that the FDA work faster to bring new drugs to market.¹¹⁰

The medical profession has lost much of its independence and most of its 20th century control over the flow of pharmaceutical information.¹¹¹ Rather than working with the government to filter pharmaceutical information, in recent years, the medical profession and biopharmaceutical sectors have joined forces to check the FDA's authority over the market dissemination of information about new drugs. Most notable is the *Washington Legal Foundation* litigation, which resulted in a federal appellate court ruling that the FDAMA provision to place quality controls on drug maker dissemination of journal articles promoting off-label use violated commercial free speech and was unconstitutional.¹¹² Drug manufacturers, though prohibited from directly marketing off-label uses of their prescription drugs, now are able to fund journals and sponsor research to generate favorable publications, and to disseminate resulting articles to doctors to encourage unapproved uses of their drugs.¹¹³ The biopharmaceutical sectors have managed to position themselves well through armies of sales representatives and aggressive sales tactics,¹¹⁴ direct-to-consumer marketing in an age of consumer-driven

¹⁰⁹ 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) (“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.”); 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 (2002).

¹¹⁰ This observation is drawn from the author's experience as Manager, Massachusetts Biotechnology Counsel in 1997-1998 and practice of law in the field of biotechnology throughout most of the 1990s.

¹¹¹ The AMA closed its own journal to advertisements for medicines under patent protection and invited the FDA as a mechanism for control. STARR, *supra* note 15, at 129.

¹¹² *Washington Legal Foundation v. Henne y*, 202 F.3d 331, 333 (C.A.D.C. 2000). Off-label use of pharmaceuticals is “generally accepted” in the medical community and commonly practiced. See *Washington Legal Found. v. Friedman*, 13 F.Supp.2d 51, 56 (D.D.C.1998) *vacated in part on other grounds*, 202 F.3d 331 (D.C.Cir.2000) (observing that “off-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine”); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349, 121 S.Ct. 1012, 1018, 148 L.Ed.2d 854 (2001).

¹¹³ See generally *See generally* INSTITUTE OF MEDICINE, *THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS* (2006) [hereinafter “IOM Report”]. Kristal M. Wicks, *Exhausted or Unlicensed: Can Field-of-Use Restrictions in Biotech License Agreements Still Prevent Off-Label Use Promotion After Quanta Computer?*, 9 U. N.H. L. REV. 157, 164 (2010).

¹¹⁴ www.bio.org. www.phrma.org. See generally Rodwin, *Drug Advertising*, *supra* note 95, at 807; Eisenberg, *New Uses*, *supra* note 96. See also , GRATZER, *supra* note 5, at 145 (“This book is not an unqualified defense of pharmaceutical companies. I am certainly ambivalent about several industry practices: the drug dinners that mix education with advertising and wine, the highly paid drug reps, the skewed studies. I meet with drug reps periodically—I need the free samples to help my patients—and I find the process uncomfortable.”). *Id.* at 145-146 (criticism of the rebirth of Prilosec as a new drug, Nexium, to overcome the end of Prilosec patent protection). The experience of Dr. Jerome Groopman is that, “Today, medicine is not separate from money. How much does intense marketing by pharmaceutical companies actually influence either conscious or subliminal decision-making? Very few doctors, I believe, prostitute themselves for profit, but all of us are susceptible to the subtle and not so subtle efforts of the pharmaceutical industry to sculpt our thinking.” GROOPMAN, *THINK*, *supra* note 2, at 9.

medicine,¹¹⁵ sponsorship of continuing medical education programs, collaboration under trade organizations such as the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Organization, and direct lobbying. The complexities of contemporary life science have raised the medical community's dependence on the drug industry for information, especially under time constraints associated with the commercialization of medicine.¹¹⁶ U.S. patients have faith in new treatments, including experimental ones.¹¹⁷

The organization and expansion of patient groups, encouraged under the U.S. pluralistic legal system and empowered 1990s information technology progress, have become another force promoting new drug approvals and an ally of the biopharmaceutical sectors in new drug development.¹¹⁸ The very mission of the FDA was changed under FDAMA to work with industry to increase its efficiency, and the agency has two decades of experience collecting user fees from drug sponsors to pay the salaries of those who review their applications.¹¹⁹ While industry and the FDA have solidified relations, drug sponsors have reduced their dependence on the American medical profession for its clinical research by turning to contract research organizations ("CROs"), private companies with global reach in the business of conducting clinical research, and moving much of it abroad.¹²⁰ The FDA also has made ongoing clinical

¹¹⁵ See generally *Symposium—Patient-Centered*, *supra* note 5. See also Wolf, *supra* note 4, at 496 ("The last few decades have seen tremendous agreement that decision-making should be a shared process but that patient preferences should rule. And that agreement prevails even when the predicted consequence of honoring the patient's wish is her death."); *id.* at 499 ("Physicians in practice are less and less surprised to see patients arrive for an office visit having researched their illness and toting internet printouts.").

¹¹⁶ As explained by Dr. Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research, drug developers have been hesitant to share genetic tests used to develop drugs with the FDA and physicians have been hesitant to uptake the tests made available. Janet Woodcock, *FDA Policy on Pharmacogenomic Data in Drug Development*, 66 LA LAW REV. 91, 93 (2005) (special symposium proceedings issue, *Genomics Revolution?*). See generally Jeffrey L. Moe, *Commercialization Considerations for Individualized Diagnostic and Drug Therapies Resulting from Pharmacogenomics*, 66 LA LAW REV. 103-116 (2005) (addressing physician resistance to uptake and other impediments to clinical use of genetic screens associated with pharmaceuticals). Even when pharmacogenomics (drug development based upon genetic variations that can promote individualized medicine) data makes it onto drug labels, the underlying sponsor data released is limited, and the medical community often lacks the knowledge to make efficient use of it. Kelly C. Lee, Joseph D. Ma, & Grace M. Kuo, *Pharmacogenomics: Bridging the Gap Between Science and Practice*, 50 J AM PHARM ASSOC. e1-e17 (2010).

¹¹⁷ See generally IOM REPORT, *supra* note 113 (suggesting black triangle indicators for new drug approvals to flag the lack of market history). See also Wylie Burke & Bruce M. Psaty, *Personalized Medicine in the Era of Genomics*, 298 JAMA 1682, 1682-84 (2007).

¹¹⁸ Previous scholarship---rise of patient groups from AZT/AIDS. Ironically, often at odds over pricing/reimbursement. See David E. Winickoff, *Governing Population Genomics: Law, Bioethics, and Biopolitics in Three Case Studies*, 43 JURIMETRICS: J. L., SCI. & TECH. 222-223 (2003).

¹¹⁹ Food and Drug Administration Modernization Act (FDAMA), Pub.L. No. 105-115, 111 Stat. 2296 (1997). See 21 U.S.C. § 355a (1997) (amended 2002); PDUFA IV, 72 FED. REG. 1743 (2007) (public comments solicited for PDUFA IV, 2008-2012). See *supra* note 8 and accompanying text.

¹²⁰ Miho Nagano, *Big Pharma Looks for a Fix*, INV. BUS. DAILY, Sept. 29, 2008 (pg. nos. unavailable online). CROs are commercial service providers that meet both basic and clinical research needs, and the business is burgeoning. See *id.* Unfortunately, guidance and enforceable law-policy to protect human subjects has not been introduced in sync with this trend: "The globalization of medical research is, in effect, quickly outpacing the development of internationally accepted ethical guidelines for the conduct of

research transparent to the general public through www.clinicaltrials.gov, further reducing dependence on the medical community.

B. DRUG UNDERDEVELOPMENT

In spite of tremendous annual increases in drug funding by industry and government over the last few decades,¹²¹ major advances in science including completion of a map of the human genome,¹²² and modernization of the Food and Drug Administration in 1997,¹²³ the U.S. drug review and approval system with heavy dependence on physician off-label use is no longer working.¹²⁴ “[T]here is substantial proof that the current method of creating medicines for the general public is problematic

research. For many medical researchers working in resource-poor countries, ethical decision-making is like sailing in the days before modern navigation; one is never quite sure where one is, or in what direction one is headed.” Daniel W. Fitzgerald & Angela Wasunna, *Away from Exploitation and Towards Engagement: An Ethical Compass for Medical Researchers Working in Resource-Poor Countries*, 33 J.L. MED. & ETHICS 559, 559 (2005). See also Stephens, *Where Profits and Lives Hang in Balance: Finding an Abundance of Subjects and Lack of Oversight Abroad, Big Drug Companies Test Offshore to Speed Products to Market*, WASH. POST, Dec. 17, 2000, at A1. See generally Michael J. Malinowski, *Ethics in a Global Pharmaceutical Environment*, 5 SANTA CLARA J. INT’L L. 57, 70-71 (2006); Jennifer M. Gold & David M. Studdert, *Clinical Trials Registries: A Reform that is Past Due*, 33 J. L. MED. & ETHICS 811 (2005) (proposing establishment of a conclusive registry for clinical trials conducted abroad); Nagano, *supra* note 120 (“A sign of the trend: In August, Princeton, N.J.-based Covance CVD, the largest U.S. CRO, struck a deal with Eli Lilly to buy Lilly’s R&D labs in Indiana for \$50 million. The deal will transfer 260 Lilly employees to Covance. Lilly also guaranteed Covance a 10-year business contract worth \$1.6 billion.”).

¹²¹ The biopharmaceutical sectors spend tens of billions of dollars on research annually. See *supra* note 30 and accompanying text; PHRMA, *supra* note 30, at iv See generally Seton Hall, The Center for Health & Pharmaceutical Law & Policy, White Paper, *Conflicts of Interest in Clinical Trial Recruitment & Enrollment: A Call for Increased Oversight* 5 (Nov. 2009).

¹²² See generally National Human Genome Research Institute, National Institutes of Health, & Department of Energy, *International Consortium Completes Human Genome Project: All Goals Achieved; New Vision for Genome Research Unveiled*, Apr. 14, 2003, available at genome.gov. (last visited Jan. 30, 2011). “Ten years after President Bill Clinton announced that the first draft of the human genome was complete, medicine has yet to see any large part of the promised benefits.” Nicholas Wade, *A Decade Later, Gene Map Yields Few New Cures*, N.Y. TIMES, June 13, 2010, at 1, 22. The transition could take many years—decades according to some commentators. See generally Braff, *supra* note 80.

¹²³ See *supra* note 108 and accompanying text.

¹²⁴ “Unfortunately, present reality is that drug development lingers between the scientifically crude, yet enormously profitable pharmaceutical past and the biopharmaceutical present and future.” Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at __ (proposing that the FDA adopt single subject research methodology to accompany its reliance on group design in human clinical research). See also 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*, CORNELL J. INT’L LAW (forthcoming) (proposing international adoption of SSRD in human clinical research and proposing a law-policy methodology to turn the “gold standard” of group design for clinical research into platinum through SSRD). For arguments in favor of changing FDA law-policy on other grounds, see generally ANGELL, *supra* note 7.

98; Peter Jennings, *Bitter Medicine: Pills Profit, and the Public Health* (2002) (ABC News); FDA, INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS (March 2004), available at <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm>.

and could prevent effective treatments from reaching the marketplace . . .”¹²⁵ As observed by Dr. Francis Collins, head of the National Institutes of Health, “[T]he drug industry’s research productivity has been declining for 15 years, and it certainly doesn’t show any signs of turning upward’ . . .”¹²⁶ The industry produced just eighteen new drugs in 2007, the lowest number in a quarter of century, twenty-four in 2008, and twenty-six in 2009.¹²⁷ Pfizer Inc., the world’s largest research-based pharmaceutical company, did not produce a single new drug approval in 2010.¹²⁸ In comparison, new drug approvals peaked in 1996 when the FDA approved fifty-three.¹²⁹

Moreover, several drugs the FDA has put on the market over the last decade have raised questions about the Agency’s judgment, effectiveness, and reliability to the point of having aroused Congressional action,¹³⁰ generated scathing reports from the Government Accountability Office and the Institute of Medicine,¹³¹ and inspired class

¹²⁵ *Braff, Patient-Tailored One*, *supra* note 80, at 5; Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at __ (forthcoming).

¹²⁶ Dr. Francis S. Collins, Director of the National Institutes of Health, as quoted in a New York Times story on the federal government’s decision to launch a billion-dollar drug development center to help industry create new pharmaceuticals. Harris, *New Center*, *supra* note 80, at A1.

¹²⁷ Steven Burrill, *Steven Burrill Predicts Biotechnology’s Fortunes for First-Half 2009*, PHARMA MARKETLETTER, Jan. 19, 2009 (pg. nos. unavailable online), 2009 WLNR 7402398 (Westlaw). The FDA approved eighteen innovative new drugs in 2007 and twenty-four in 2008. *Id.* But see Miho Nagano, *Big Pharma Looks for a Fix*, INV. BUS. DAILY, Sept. 29, 2008 (pg. nos. unavailable online) (stating 17 approvals in 2007). Jenna Greene, *Has Obama Redirected the Regulatory System? After One Year, Some Agencies Can’t Write Rules Fast Enough, While Others Sit and Wait*, NAT’L L. J., Jan. 18, 2010, at p. 11. The FDA approved twenty-four innovative new drugs in 2008 and eighteen in 2007. See Jared A. Favole, *FDA Approved More Drugs in 2008*, WALL. ST. J., Jan. 2, 2009, at A9.

¹²⁸ Pfizer Inc., Official Site, <http://www.pfizer.com/about/?gclid=CMGcjqWm36UCFQGe7Qod4WH9VA> (last visited Aug. 1, 2011).

¹²⁹ Robert Coopman, *Drug Makers in Midst of Productivity Quandry*, CHAIN DRUG REV., Jan. 18, 2010, p. 42, 2010 WLNR 2155205.

¹³⁰ The culmination of Congressional concern is the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823 (Sept. 27, 2007) (codified as amended in scattered sections of 21 U.S.C.).

¹³¹ See generally UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE, REPORT TO CONGRESSIONAL REQUESTERS, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS (2006) [hereinafter “GAO FDA REPORT”]; IOM REPORT, *supra* note 113. 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 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 *Discourse*, *supra* note 20, at 2-24. During the span of the career of a single academic researcher, 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.*

action litigation.¹³² The public has lost confidence in the FDA, and for good reason.¹³³ The FDA withdrew ten drugs for safety concerns between 2000 and March 2006,¹³⁴ and “It 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.”¹³⁵ Vioxx is probably the agency’s most notorious mistake—“a ‘scarlet letter’ the FDA is likely to wear for years to come.”¹³⁶ In the fall of 2010, the FDA itself “concluded that in some cases two types of drugs that were supposed to be preventing serious medical problems were, in fact, causing them.”¹³⁷ One was Avandia, which was prescribed heavily to treat type-2 diabetes. An association was made between Avandia and 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.¹³⁸ The second was bisphosphonates—an active agent in the prescription drugs Fosamax, Actonel and Boniva, which were prescribed frequently to prevent fractures common in people with osteoporosis. Bisphosphonates, prescribed to prevent bone loss, was determined to actually *cause* thigh bone fractures and jawbone degeneration.¹³⁹ In addition, in 2009 it was determined that Acutane, on the market since 1982, subjected an entire generation of teenagers who were prescribed the drug to treat severe acne to increased risks for inflammatory bowel disease, ulcerative colitis, Crohn’s disease, other gastrointestinal disorders, liver damage, birth defects, and

¹³² See generally Thomas, *Vioxx Story*, supra note 7.

¹³³ “Public confidence in FDA fell from 80% in the 1970s to 61% in 2000; 56% in 2004; and 36% in 2006.” Evans, *Seven Pillars*, supra note 46, at 431. See Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 443 (2008), citing Bill Hubbard & Steven Grossman, Harris Poll Survey (Apr. 11, 2007).

¹³⁴ GAO FDA REPORT, supra note 131, at 10. See Evans, *Seven Pillars*, supra note 46, 428-431.

¹³⁵ BENGT D. FURBERG & CURT D. FURBERG, *EVALUATING CLINICAL RESEARCH* 8 (2d ed. 2007).

¹³⁶ Thomas, *Vioxx Story*, supra note 7, at 365; Nagano, supra note 120 (pg. nos. unavailable online) (the Vioxx controversy has inspired drug companies to undertake more toxicology studies).

¹³⁷ Gina Kolata, *When Drug Problems Cause Problems They Are Supposed to Prevent*, N.Y. TIMES, Oct. 17, 2010, p. 17.

¹³⁸ *Id.* Avandia triggered an expansive U.S. Senate Finance Committee inquiry and bipartisan report highly critical of both GlaxoSmithKline (GSK) and the FDA. See Committee on Finance, United States Senate, Staff Report on Glaxosmithkline and the Diabetes Drug Avandia (Jan. 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.* It caused 83,000 heart attacks between 1999 and 2007 according to the FDA’s own estimates. *Id.* “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.” *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.* GSK responded by defending Avandia. *Id.* GSK is undertaking another round of clinical trials, but those will not be completed until 2020. *Id.* 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*, 16 FDA WEEKLY (Feb. 26, 2010) (pg. nos. unavailable online), available at 2010 WLNR 4078219. This suggestion was made years earlier, including in the 2006 Institute of Medicines Report on the FDA and in the law literature. See generally IOM REPORT, supra note 117. See Thomas, *The Vioxx Story*, supra note 7, at 365.

¹³⁹ Kolata, *Drug Problems*, supra note 137, at 17.

suicidal thoughts. Roche, the manufacturer, pulled Acutane from the market on June 29, 2009.¹⁴⁰

Many commercial drug developers and their supporters attribute the drop-off in new drug approvals to over-regulation by the FDA and other government entities.¹⁴¹ Others attribute the fall to an industry that is clinging to the low science and regulatory standards of the past, making bad and expensive decisions based upon these low standards,¹⁴² stretching the commercial lives of pharmaceuticals through manipulation of the patent system, and contriving “me too” drugs rather engaging in genuine innovation.¹⁴³ The Vioxx controversy did force the agency to raise its level of scrutiny, including more toxicology studies and now measures to comply with the FDAAA.¹⁴⁴

A factor contributing to the drug industry’s underperformance is that, subsequent to enactment of FDAMA in 1997 (again, drug approvals peaked in 1996), the FDA has been relying even more on market experience for meaningful clinical understanding of

¹⁴⁰ Drug Watch, Accutane, <http://www.drugwatch.com/accutane/> (last visited Mar. 2, 2011) (stating that approximately 5,000 personal injury lawsuits have been filed against Roche).

¹⁴¹ See generally Thomas, *Vioxx Story*, *supra* note 7. 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.

OVERDOSE, *supra* note 60, at 239. Dr. Gratzner 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*, *supra* note 5, at 152.

¹⁴² See generally Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16.

¹⁴³ See Thomas, *Vioxx Story*, *supra* note 7, at 366. See generally ANGELL, *supra* note 7; Jamie L. Aldes, *The FDA Clinical Trial Process: Effectuating Chance in the Regulatory Framework Governing Clinical Trials to Account for the Historical Shift from “Traditional” to “New” Phase I Trials*, 18 HEALTH MATRIX 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.”). Aldes, *supra*, at 463 (internal footnotes omitted). 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, “[c]onsumers 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.”

Aldes, *supra*, at 463 (internal footnotes omitted).

¹⁴⁴ See generally Thomas, *Vioxx Story*, *supra* note 7. See also FDAAA, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.). See *infra* notes 144, 165-167, 170, 188-200 and accompanying text (FDAAA).

pharmaceuticals and off-label physician use for drug discovery. Specifically, under FDAMA, the FDA lowered its approval standard by switching its presumption in favor of safety—errring on the side of safety since—to one that favors approval on the condition of Phase IV studies under section 506B of FDAMA, often referred to as 506B studies.¹⁴⁵ The intention is good and consistent with the efficiency element of the FDA’s mission infused by FDAMA: make new drugs available to patients who need them as quickly as possible.¹⁴⁶ The problem is that the FDA has not been enforcing these post-market study conditions.¹⁴⁷ Once on the market, the new drug not fully understood becomes an off-label prescription option.

Folding pharmaceuticals into the context of the overall practice of medicine raises more issues. Medicine remains much more art than 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%.¹⁴⁸

¹⁴⁵ 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. *See* Food and Drug Administration, *SEC. 506B. [21 USC §356b] Reports of Postmarketing Studies*, available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/FDCAActChapterVDrugsandDevices/ucm109170.htm> (last visited Oct. 10, 2010); Thomas, *Vioxx Story*, *supra* note 54, at 367. The purpose of Phase IV (on-the-market) studies is to probe lingering questions and to perfect clinical use. *See* HUTT & MERRIL, & GROSSMAN, *supra* note 47, at 734-738.

¹⁴⁶ 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) (“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.”); 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 (2002).

¹⁴⁷ *See generally* UNITED STATES GOVERNMENT ACCOUNTABILITY OFFICE, *DRUG SAFETY: IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS* (Mar. 2006); INSTITUTE OF MEDICINE, *THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS* (Sept. 2006). More than 144 drugs have reached the market conditionally since 1992. *See generally* GAO REPORT, *supra* note 146; GOVERNMENT ACCOUNTABILITY OFFICE, *DRUG SAFETY: FDA HAS BEGUN EFFORTS TO ENHANCE POSTMARKET SAFETY, BUT ADDITIONAL ACTIONS ARE NEEDED* (NOV. 9, 2009). 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, *POSTMARKET SAFETY*, *supra* note 161. 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. For example, Shire Laboratories 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. GAO REPORT, *supra* note 146; IOM REPORT, *supra* note 146.

¹⁴⁸ Carey, *Medical Guesswork*, *supra* note 6 (page nos. unavailable online), 2006 WLNR 8974827 (reporting on the movement for evidence-based medicine). *See generally* ANGELL, TRUTH, *supra* note 7. An important study released in 1995, confirming studies based upon autopsies done before, indicated that

Inviting the practicing physician community to experiment with new pharmaceuticals off-label and, especially in the case of pharmaceuticals that reach the market under 506B, to work out the clinical safety and efficacy of drugs over time, patient-by-patient, “exposes patients to potentially harmful drug interactions and delays potentially effective or the ‘right’ treatment.”¹⁴⁹ At most, only one-third of prescription medicines act as expected when prescribed to patients.¹⁵⁰ Adverse drug reactions cause more than 100,000 deaths and more than two million hospitalizations annually in the US—meaning that more people in the U.S. die from legal use of prescription medications than from automobile accidents.¹⁵¹

The crude science past of just taking away symptoms is fading into the history of drug development. Genomics (genetic expression) already has a strong presence in the drug development pipeline; scientists are “working at the cellular, genetic, and molecular levels in living organisms to identify genetic expression, to reveal the origins and progression of disease, and to make connections between the two and develop drugs

15 percent of all diagnoses are inaccurate, and the advent of genomics has made the practice of medicine more complicated since then. GROOPMAN, THINK, *supra* note 2, at 24. 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.

GROOPMAN, *supra* note 2, at 5, 7 (2008).

¹⁴⁹ Need to shift single subject from delivery of care to drug development: Braff, *Patient-Tailored One*, *supra* note 80, at 28.

¹⁵⁰ See generally IOM REPORT, *supra* note 113. See Bd. on Health Care Servs., Inst. of Med., Preventing Medication Errors 5 (Philip Aspdin et al. eds., 2006) (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 also Braff, *Patient-Tailored One*, *supra* note 80, at 9, 16-17. Efficacy failure may be as high as 60% of prescriptions. Evans, *Seven Pillars*, *supra* note 46, at 498. 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 laced 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); Braff, *Patient-Tailored One*, *supra* note 80, 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. Thurmman, *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: A Systematic Review*, 286 JAMA 2270, 2270-79 (2001).

¹⁵¹ Barkur Sriram Shastry, *Pharmacogenetics and the Concept of Individualized Medicine*, 6 PHARMACOGENOMICS J. 16, 16-21 (2006).

based upon those connections.”¹⁵² Although the underlying science has shifted in the direction of genetic precision over the last few decades, law-policy norms and standards have not evolved in a commensurate fashion: “Under the present law-policy scheme, drug review is too lenient, practical understanding of new pharmaceuticals is too limited, and market approval invites excessive off-label use—an approach that muddles clinical care with clinical research excessively, and exacerbates the unpredictability of prescription medications.”¹⁵³

In addition to its nature, *how* drug development science is done has changed intrinsically over the last few decades. Contemporary drug development necessitates collaboration among government, academia and industry—often collaboration among competitors—and vast commercial investment.¹⁵⁴ In the words of one observer, U.S. law and policy that promotes the commercialization of government-funded basic research “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.”¹⁵⁵ Commercialization necessitates strong intellectual property protection, which has detonated an explosion of material transfer and confidentiality and disclosure agreements and shrouded science in secrecy to the detriment of the public nature of science that was the governing academic research norm during the decades before.¹⁵⁶ Also, “The science publications depended upon for scrutiny, accountability, and human health assessment too have embraced commercialization—evident by conflicts of interest controversies and the journals’ imposition of high cost barriers to access their publications.”¹⁵⁷ Moreover, industry has augmented its influence over both government and the general public expansively during the last few decades—

¹⁵² See Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at __ (forthcoming). See also Evans, *Seven Pillars*, *supra* note 46, at 462-468. See generally 000 *Genomes Project: Press Release, International Consortium Announces the 1000 Genomes Project*, available <http://www.1000genomes.org/>, last visited May 4, 2009 (international consortium formed to research genetic variation); Braff, *supra* note 80; Ctr. for Genetics Educ., *The Human Genetic Code--The Human Genome Project and Beyond* (2007), available at www.genetics.com.au/pdf/factsheets/fs24.pdf (noting diagnosis and predictive testing for genetic conditions); Peter Imming, Christian Sinning, & Achim Meyer, *Drugs, Their Targets, and the Nature and Number of Drug Targets*, 5 *Nature Reviews Drug Discovery* 821-824 (Oct. 2006) (page nos. not available online), available at <http://www.nature.com/nrd/journal/v5/n10/full/nrd2132.html> (last visited June 21, 2009). See generally, *Genomics Revolution?*, *supra* note 79, at 1-143.

¹⁵³ Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at __ (forthcoming). See generally Malinowski & Gautreaux, *Gold Does Not Glitter*, *supra* note 124.

¹⁵⁴ “Remaining at the forefront of technology is innate to universities’ combined missions of teaching, research, and service”, meaning that integration among academic, industry and government in biomedicine was inevitable. See Hughes, Jakimo, & Malinowski, *supra* note 20, at 399.

¹⁵⁵ See Lorelei Ritchie de Larena, *The Price of Progress: Are Universities Adding to the Cost?*, 42 *HOUS. L. REV.* 1373, 1375, 1378 (2007). For another evaluation of Bayh-Dole, see David C. Mowery, Richard R. Nelson, Bhaven Smpat & Arvids Ziedonis, *IVORY TOWER AND INDUSTRIAL INNOVATION: U.S. UNIVERISTY-INDUSTRY TECHNOLOGY TRANSFER BEFORE AND AFTER THE BAYH-DOHL ACT* (2004).

¹⁵⁶ “Aggressive integration of academia and industry has created a proliferation of conflicts of interest, and the public nature of science—collegiality, communication, transparency, and accountability—has shifted in the direction of secrecy.” Malinowski, *Drug Puberty?*, *supra* note 20, at text accompanying n167.

¹⁵⁷ *Id.* at text accompanying note 168.

the former over its lobbying presence,¹⁵⁸ user fees paid to finance the FDA review of its products,¹⁵⁹ and alliances with patient groups and the medical profession,¹⁶⁰ and the latter through aggressive direct-to-consumer marketing.¹⁶¹ Secrecy prevails, reliability of the peer review mechanism is unreliable, and the integrity of research is subject to question:¹⁶²

The vast capacity to publish research and to share knowledge is tainted by conflicts of interest which threaten the reliability and integrity of the peer review process and, consequently, the underlying research. Governments, professional societies, and most science journals have failed to introduce the mechanisms necessary to manage conflicts of interest in an era of aggressive commercialization with meaningful confidence.

Arguably, “government interventions are necessary to protect and preserve the public nature of science, which is essential to shore up the contemporary science enterprise.”¹⁶³

Both Congress and the current administration are concerned enough about the state of drug development to take action. The Obama Administration has announced formation of a new center, funded with a billion dollars, to help private industry develop new drugs under the direction of Francis Collins, the present Director of NIH and leader of the government effort to map the human genome.¹⁶⁴ Congress enacted the Food and Drug Administration Amendment Act of 2007 (FDAAA)¹⁶⁵ —“the most momentous shift in drug regulation in half a century.”¹⁶⁶ Under the FDAAA, premarket clinical studies are augmented and evidentiary standards demand culling more data from them, but their limitations also are recognized. FDAAA calls for the FDA to establish an expansive postmarket risk identification and analysis Internet-based system, known as the Sentinal Network, to disseminate risk information to patients and health care providers in an ongoing manner.¹⁶⁷

¹⁵⁸ The PDUFA legislation and user fee system are addressed infra in notes 108-110, 119, and the accompanying text. Commentators have estimated that there are as many as four lobbyists working in Washington, DC on behalf of the pharmaceutical sector for every member of Congress. *Who's Sick in America?*, 20/20, ABC News (2006); ANGELL, *supra* note 7. *See generally* Thomas, *Vioxx Story*, *supra* note , at 365.

¹⁵⁹ *See supra* notes 110, 118 and accompanying text.

¹⁶⁰ *See supra* notes 8, 119 and accompanying text.

¹⁶¹ *See supra* notes 5, 115 and accompanying text.

See supra notes ___ and accompanying text.

¹⁶² *See generally* Malinowski, *Discourse*, *supra* note 20, at 2-24.

¹⁶³ *Id.* at 23.

¹⁶⁴ *See* Gardiner Harris, *New Federal Research Center Will Help Develop Medicines*, N.Y. TIMES, Jan. 23, 2011, at A1.

¹⁶⁵ Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

¹⁶⁶ Evans, *Seven Pillars*, *supra* note 46, at 423. *See generally id.*; Barbara J. Evans, *Authority of the Food and Drug Administration to Require Data Access and Control Use Rights in the Sentinel Data Network*, 65 FOOD & DRUG L. J. 67 (2010).

¹⁶⁷ FDAAA, § 915, 21 U.S.C.A. § 355(r) (West Supp. 2009). *See generally* FDA, *The Sentinel Initiative : An Update on FDA's Progress in Building a National Electronic System for Monitoring the Postmarket Safety of FDA-Approved Drugs and Other Medical Products* (July 2010), available at

IV. A LAW-POLICY PRESCRIPTION

The practice of medicine and drug R&D have changed immensely over the last half century,¹⁶⁸ but excessive physician discretion to prescribe medications off label lingers on—to the detriment of drug innovation and human health.¹⁶⁹ The Institute of Medicine, the Government Accountability Office, the National Institutes of Health, and Congress have recognized this prescription drug dilemma—culminating in the FDAAA and the new billion-dollar government research center that will attempt to resurrect drug research abandoned by industry.¹⁷⁰ Physician autonomy, including discretion to prescribe drugs off label, dates back to the establishment of the drug application approval requirement in the 1960s,¹⁷¹ and the two complemented each other for decades.¹⁷² Times have changed: broad discretion to prescribe off label is inconsistent with the reality of contemporary drug development and the delivery of health care.¹⁷³

Although science is shifting in the direction of genetic precision, the drug development pipeline is lengthy and winding, and the transition is ongoing and incomplete.¹⁷⁴ Some element of physician discretion to prescribe off-label is necessary during the evolution of drug development science into the genomics era, but the historic level invites a race to the bottom—both in medicine and drug development.¹⁷⁵ The standard for delivery of care must be modified and the regulatory standard for new drug approvals must be raised so that more drug discovery is shifted from clinical care to clinical research. Variables driving the need for this law-policy change include contemporary science capabilities, the proliferation of adverse drug events, drug ineffectiveness, the need to choose among treatment options, the increasing complexity of biopharmaceuticals, health care cost pressures, and the vulnerability of patients—

<http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf> (last visited July 17, 2011);

Evans, *Seven Pillars*, *supra* note 46; Evans, *FDA Authority*, *supra* note 166.

¹⁶⁸ See generally STARR, *supra* note 15; GROOPMAN, *supra* note 2.

¹⁶⁹ See *supra* Part III.

¹⁷⁰ See *supra* notes 130 and accompanying text (FDAAA); 113 (IOM REPORT); 131 (GAO REPORT).

¹⁷¹ See *supra* note 46 and accompanying text.

¹⁷² See generally *supra* Part III.. See Evans, *Seven Pillars*, *supra* note 46, at 502. As explained by Professor Evans,

To ensure individual efficacy, the agency seemingly would need a mechanism for enforcing physicians' compliance with its approved product labeling. In 1962, Congress was unwilling to assert that federal jurisdiction extended that far. In fairness, Congress's decision did not significantly diminish public health or safety: The science of that day would not have supported meaningful regulation of individual effects, even if Congress had been comfortable with the jurisdictional issues it presented.

Id.

¹⁷³ *Id.* at 504-505 (cross-labeling to couple genetic screens with drugs) . See generally *supra* Part III.

¹⁷⁴ See generally Braff, *Patient-Tailored One*, *supra* note 80; Braff, *Patient-Tailored Two*, *supra* note 80; BIOTECHNOLOGY INDUSTRY ORGANIZATION, GUIDE TO BIOTECHNOLOGY (2008), available at <http://www.bio.org/speeches/pubs/er/>. For information about the biopharmaceutical sectors, visit the Internet sites of the industries' trade organization, PhRMA, www.org (last visited Mar. 1, 2011).; BIO, www.org (last visited Mar. 1, 2011). Both drug developers and physicians have demonstrated hesitation towards pharmacogenomics. See generally Woodcock, *Pharmacogenomic Data*, *supra* note 116; Moe, *Pharmacogenomics*, *supra* note 116.

¹⁷⁵ See *supra* Part III.

seekers of care, not research participants under the scrutiny of regulations to protect human subjects.¹⁷⁶

Several trends suggest that such law-policy change is inevitable, and that drug sponsors should expect more scrutiny and demands for accountability from regulators, the medical community, and the general public. These trends include rising health care finance pressures, federal and state, domestic and international;¹⁷⁷ increased transparency of market performance and market behavior through internet communication, including organized observation through patient and consumer protection groups; and pressure on the FDA to increase post-marketing regulation requirements and general enforcement.¹⁷⁸ However, given the extent to which physician discretion over use of prescription pharmaceuticals is entrenched in the legislation enabling the FDA¹⁷⁹ and has been affirmed and assured repeatedly, including in the enactment of FDAMA,¹⁸⁰ comprehensive direct limitations on physician discretion to prescribe off-label would require an expansive law-policy intervention and invite legal challenges.¹⁸¹ Any such proposal would trigger united opposition from the physician community and the biopharmaceutical sectors with their expansive lobbying resources.¹⁸² Similarly, using the regulatory process to attempt to impose commercial uses on new drug candidates or specific types of human clinical trials on drug developers would invite allegations of undue impediment on the commercial freedom that is the touchstone of our private market system and introduce susceptibility to legal challenges.¹⁸³

¹⁷⁶ See the Common Rule, 45 C.F.R. Part 46; FDA 21 CFR Parts 50, 56 (FDA human subject protections). For more information about the protection of human subjects, visit the Internet site of the Office for Human Research Protections (OHRP), <http://www.hhs.gov/ohrp/> (last visited Aug. 1, 2011).

¹⁷⁷ See generally PWC REPORT, *supra* note 5.

¹⁷⁸ See FDA, STAGNATION?, *supra* note 124.

¹⁷⁹ See *supra* notes 48-49 and accompanying text.

¹⁸⁰ The House Report that accompanied FDAMA expressly states that “FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-label uses of approved drugs is not within the jurisdiction of the FDA.” H.R.Rep. No. 105-310, at 60 (1997).

¹⁸¹ “The drug development regulatory regime embodies deference to commercial free speech, proprietary interests, profit incentives, and the discretion to practice medicine—as the FDA has been reminded by Congress and through several legal challenges during the genomics revolution.” Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at ___ (forthcoming). For example, the biopharmaceutical sectors and physician community joined forces to successfully challenge the efforts of the FDA to regulate two pharmaceutical strategies to promote off-label use—dissemination of science publications to physicians (referred to as “enduring materials”), and continuing medical education (CME) programs for doctors that profile off-label uses. See generally *Washington Legal Foundation v. Henney*, 202 F.3d 331 (C.A.D.C. 2000). The Court of Appeals for the District of Columbia determined that the relevant FDAMA provisions imposed an undue burden on commercial free speech in violation of the First Amendment. See *id.* at ___. Also, in 2006, the U.S. Supreme Court ruled in that federal law does not prohibit Oregon doctors from prescribing lethal doses of drugs, thereby striking down a key challenge to the Death with Dignity Act. *Gonzales v. Oregon*, 54 U.S. 243 (2006).

¹⁸² See *supra* note 158 (industry lobbying resources); *Washington Legal Foundation*, *supra* note 181.

¹⁸³ Cf. EPSTEIN, OVERDOSE, *supra* note 60. See, e.g., *Association of American Physicians and Surgeons Inc., et al. v. United States Food and Drug Administration*, 226 F.Supp.2d 204 (Oct. 17, 2002), 2002 WL 31323411 (D.D.C.). See *infra* note 103 and the accompanying text (challenge to FDA rules proposing mandatory pediatric trials). However, in recent years, Congress did succeed in banning a medical

There are several more viable law-policy options, each of which is addressed below. The first is to fully utilize the FDAAA to generate earlier and more complete information about new drugs under direct FDA oversight. This approach, coupled with greater FDA enforcement of existing market checks and utilization of the added market control mechanisms introduced by the FDAAA, would leave physicians with less off-label discretion. Another option is to raise the technical clinical trial science standard for drug approval and post-market clinical trials to generate more information about drugs through the regulatory process. This added information would be fodder to raise the drug approval standard and utilize market use restrictions, including those under the FDAAA, which would force drug sponsors to rely less on off-label use and marketing. Given that market return drives the commercial biopharmaceutical sectors, another option is to condition reimbursement for off-label uses of pharmaceuticals under Medicare and Medicaid, in the health insurance plans covering federal employees, and through national health care reform.

A. RAISE THE SCIENCE STANDARD

The biopharmaceutical sectors have the resources and capabilities to meet a higher science standard in clinical research. Although the profits of yesterday's investors will not pay for today's and tomorrow's drug development, the pharmaceutical industry has been *the* most profitable sector for well over a half century, and today's biopharmaceutical sectors have tremendous resources and invest tens of billions in drug R&D annually.¹⁸⁴ In fact, arguably adhering to a science standard that is too low is wasting their vast resources through poor decision making, failures, class action litigation, and lost opportunities in drug development.¹⁸⁵ Moreover, although drug developers spend tens of millions of dollars on research, they spend more on marketing—and much of that to encourage physicians to exercise their discretion to use their drugs off label.¹⁸⁶

The imposition of a higher science standard in clinical research could be a means to raise the level of discovery in premarket drug development and deliver drugs to market with more direction and less physician off-label discretion. The low hanging fruit in drug development is gone, science is much more complicated, and a more rigorous science standard for clinical research is needed to reach higher.¹⁸⁷ Approaches could center on

procedure, partial birth abortion, based upon its assessment that the procedure was not medically necessary. *Gonzales v. Carhart*, 550 U.S. 124 (2007) (upholding the Partial-Birth Abortion Act of 2003).

¹⁸⁴ ANGELL, TRUTH, *supra* note 7, at 135-172.

¹⁸⁵ See Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at ___ (forthcoming). For discussion of industry's investment in drug development and difficulties producing in recent years, see *supra* Part III.B.

¹⁸⁶ ANGELL, TRUTH, *supra* note 7, at 135-172. Much drug marketing is to encourage the medical community to exercise its discretion to use their products off-label. Harris Meyer, *Medicine: Costly Stamp of Approval*, L.A. TIMES, Jan. 18, 2010, at p. 3, available at 2010 WLNR055167. According to an FDA estimate, almost two percent of all prescription drugs are directly marketed without its approval, meaning illegally. Harris Meyer, *Medicine: Costly Stamp of Approval*, L.A. TIMES, Jan. 18, 2010, at p. 3, available at 2010 WLNR055167.

¹⁸⁷ EPSTEIN, OVERDOSE, *supra* note 60.

the scope of clinical research required, a content-driven standard for human clinical research, or a combination of the two.

Congress has recognized the drug underdevelopment problem and has mandated a higher science standard through the FDAAA, but its solution is to do more with the same technical human clinical trials methodology.¹⁸⁸ The core methodology of the FDAAA, still to be fully implemented, is to expand clinical studies before market approval and to extensively augment market data collection from and dissemination of information to physicians through Sentinel, an expansive data collection and dissemination system among the FDA, physicians, and patients.¹⁸⁹ A plain reading of the FDAAA, which opens many possibilities subject to implementation,¹⁹⁰ is a level of acceptance of the limitations of the clinical trial process that puts drugs on the market, though the FDAAA will expand that process,¹⁹¹ and belief that drawing more information from the physician-patient experience into the regulatory process with enhanced FDA market presence will shore up the reliability of prescription drugs.¹⁹² To juxtapose the present with the FDAAA future, the core FDAAA approach calls for more of the same in clinical trials before the FDAAA,¹⁹³ and essentially pushes physicians and their patients even more into a research mode outside the scope of regulations to protect human subjects.¹⁹⁴ To establish the Sentinel network and achieving the extensive physician participation the approach is premised upon is a lofty, arguably unrealistic, goal in the foreseeable future, especially given the discretion allotted physicians over prescription drugs, federal and state medical privacy laws, and the proprietary nature of the information at issue, and cost.¹⁹⁵ As explained by Professor Evans,¹⁹⁶

¹⁸⁸ Technical science methodology for clinical trials is addressed in Malinowski & Gautreaux, *supra* note 16, at Part II.A.

¹⁸⁹ See *supra* notes 189, 195-200 and the accompanying text.

¹⁹⁰ See *infra* notes 188-198 and the accompanying text.

¹⁹¹ Congress has attempted to shift traditional Phase IV trials into premarket studies through the FDAAA. Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.); see generally Evans, *Seven Pillars*, *supra* note 46. Phase IV studies have been largely observational and centered on post-marketing surveillance to detect and define previously unknown or inadequately quantified adverse reactions and related risk factors. Post-marketing surveillance is sometimes referred to as “Phase V” trials. See Jaime 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, 472 (2008) (“Phase V trials monitor the effects of the drugs as reported by physicians, survey data, and discover new uses for the drug.”). In recent years, they often have distinguished defined demographic groups that may have been overlooked as a focus point during the trials that put the drugs on the market. See generally Braff, *Personalized Medicine Part II*, *supra* note 80.

¹⁹² See generally Evans, *Seven Pillars*, *supra* note 46; Evans, *Authority*, *supra* note 166.

¹⁹³ Increasing the scope of human clinical trials exponentially over the last five years has resulted in less, not more, drug approvals, and clinical trial desperation has exploded the scope and cost of Phase III trials. See generally Nagano, *supra* note 20. See also Malinowski & Gauteaux, *Methodology*, *supra* note 16, at 73-77 and the accompanying text.

¹⁹⁴ Increasing the scope of human clinical trials exponentially over the last five years has resulted in less, not more, drug approvals. See *supra* notes 125-129 and accompanying text.

¹⁹⁵ See generally Evans, *Seven Pillars*, *supra* note 46, at 496. See also Barbara J. Evans, *Congress’ New Infrastructural Model of Medical Privacy*, 84 NOTRE DAME L. REV. 585 (2009) (discussing FDA reliance on voluntary regulatory compliance in the context of FDAAA regulatory infrastructure).

Frankly, the concern is not whether FDA will over-share access to Sentinel data. The concern is that FDA may fail to ensure the level of access Congress envisioned. In recent years FDA has tended to favor a consensual model of regulation, a sort of regulation by consent of the regulated, and has shown a certain reluctance to flex compulsory power.

The provisions of the FDAAA that call for the FDA to pull more discovery into the premarket approval process and then approve market use with many more conditions on physician use is not consistent with the known realities of drug discovery and delivery—which depends heavily on learning from the physician-patient experience.¹⁹⁷ She also approaches the FDAAA with thoughtful practicality and raises numerous considerations about the implementation of Sentinel.¹⁹⁸ A fundamental weakness in the FDAAA is that its Sentinel approach assumes a metamorphosis in the culture of the practice of medicine—a change in entrenched norms that make broad off-label discretion dangerous to human health. In sum, the vast majority of practicing physicians are not clinical researchers, and the disciplines are wholly distinguishable when it comes to handling information. As explained by Dr. Davit Gratzer, the Sentinel approach works well in theory,¹⁹⁹ however there is a strong reality to overcome:²⁰⁰

Doctors are reluctant to take the time to fill out lengthy drug safety reports. Some have estimated that under 1 percent of adverse events are reported by doctors. Indeed, the FDA has so little confidence in safety information coming from physicians' offices that they have a full-time staff whose job it is to read medical journals for letters about drug reactions, figuring that doctors are actually more likely to write to a journal than to the FDA. Meanwhile, drug companies seem to do the opposite, flooding the FDA with any and every possible adverse reaction, burying significant events in a graveyard of data. This over-reporting creates distracting noise. On top of this, the FDA largely doesn't monitor post-approval side effects anyway.

¹⁹⁶ Evans, *Seven Pillars*, *supra* note 46, at 496. *See also* Evans, *New Infrastructural*, *supra* note 195, at 585 (discussing FDA reliance on voluntary regulatory compliance in the context of FDAAA regulatory infrastructure).

¹⁹⁷ *See generally* Evans, *Seven Pillars*, *supra* note 46; Evans, *Authority*, *supra* note 166. However, Professor Evans does challenge the off-label norm as an antiquated hold-over from last century. *See* Evans, *Seven Pillars*, *supra* note 46, at 509.

¹⁹⁸ *See generally* Evans, *Seven Pillars*, *supra* note 46; Evans, *Authority*, *supra* note 166.

¹⁹⁹ GRATZER, *supra* note 5, at 158. Dr. Gratzner acknowledges that doctors do not report about pharmaceuticals, but he still proposed that heightened electronic surveillance could improve drug delivery:

If a new drug is launched that has a certain rare toxicity to the liver, a real-time surveillance network might eventually be able to detect subtle elevations in the liver enzyme tests of patients who were started on the drug and also happened to have blood work done around the same time. If enough of these signals were detected, it might alert the FDA that there is a potential liver toxicity and allow the agency to intervene before real harm is done to any patients.

Id.
²⁰⁰ *Id.*

Another reality is that the FDA's technical science standard for human clinical trial research is too low, which causes second-guessing by the agency in the marketplace and failure in the context of aggressive drug sponsor marketing to excessive physician discretion.²⁰¹ As explained by Dr. Gratzner,

In other words, despite the extraordinary caution of the FDA, it's difficult to tell exactly how a drug affects people until it hits pharmacies. Bromfenac is a case in point. No problems had been discovered by the original clinical trials, involving 2,500 people. The analgesic was withdrawn after causing four deaths and necessitating eight liver transplants—but the medication was taken by 2.5 million people.²⁰²

The FDA could raise its technical science standard by complementing the global gold standard for clinical research, group design (GD), with a single subject research design methodology (SSRD):²⁰³

GD is based in randomized, parallel, group trials. While GD typically focuses on ascertaining statistically significant variations based upon group averages, the core SSRD methodology is to repeat comparisons of control and treatment conditions with the same individual or staggered across similar individuals, graph the data on a subject-by-subject basis, and analyze the results. Thus, the individual serves as her own control while the variables interacting between the individual and the environment are isolated.

GD depends “upon mathematical abstracts that, although representative of the group collectively, may say nothing decisive about members of the group individually, let alone broad populations of patients with health care needs outside the group.”²⁰⁴ As explained by Dr. Gratzner:²⁰⁵

Call it the post-Vioxx conventional wisdom: the belief that approval standards must

²⁰¹ See generally Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16.

²⁰² GRATZNER, *supra* note 5, at 157.

²⁰³ See generally Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16. This SSRD proposal was introduced and fully discussed in Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16. The discussion was extended to propose international adoption of SSRD in human clinical research through the International Conference on Harmonisation (ICH)—an advisory body for drug harmonization for the European Union (EU) through the European Medicines Agency (EMA), the US through the FDA, and Japan through the Ministry of Health, Labor, and Welfare, and industry leadership in each market. See generally Malinowski & Gautreaux, *Global Gold*, *supra* note 124. For information about ICH, visit its official web site, <http://www.ich.org/cache/compo/276-254-1.html> (last visited July 2010). The ICH recognizes GD as the global gold standard for human clinical research. See generally International Conference on Harmonisation (ICH) in *E9 Statistical Principles for Clinical Trials*. ICH issued *E9* in 1998 to harmonize statistical methodologies used to support marketing applications. *ICH Guidance Examines Statistical Principles to Support Clinical Research*, GUIDE TO GOOD CLINICAL PRACTICE NEWSLETTER (Nov. 1998); 63 FED. REG. 49583-49597 (Sept. 16, 1998). ICH Michael J. Malinowski, *Ethics in a Global Pharmaceutical Environment*, 5 SANTA CLARA J. INT'L L. 57, 70-71 (2006).

²⁰⁴ Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at __ (forthcoming).

²⁰⁵ GRATZNER, *supra* note 5, at 156-157.

be toughened up to ensure that America's drugs are safe. Indeed, many demand that the FDA require more clinical trials on greater number of participants, with the logic that the system has failed spectacularly so we should embrace the system more zealously. Here's the FDA's dirty little secret: clinical trials involve a relatively homogenous group of healthy individuals who collectively are totally unrepresentative of the people who actually take pharmaceuticals. The FDA doesn't need to raise the bar higher, it needs to rethink drug safety.

Abstracts based on group averages put drugs on the market, "But, in fact, few if any physicians work with this mathematical paradigm. The physical examination begins with the first visual impression in the waiting room, and with the tactile feedback gained by shaking a person's hand. Hypotheses about the diagnosis come to a doctor's mind even before a word of the medical history is spoken."²⁰⁶

SSRD would heighten appreciation for human variability and individuality, innate to the practice of medicine, in the human clinical research that puts and keeps drugs on the market.²⁰⁷ A major practical advantage of SSRD over GD is that "It overcomes some of the inherent limitations found in large-scale clinical trials, in that treatments are tailored for unique individuals and can also be modified over time."²⁰⁸ SSRD could be implemented in conjunction with FDAAA, especially through the latter's provisions that require much more detailed information gathering and interface with physicians for Phase IV trials and market use.²⁰⁹ This union could be extremely beneficial to the practice of medicine directly, as well as through improvements to drug development:²¹⁰

Research supports the effectiveness of the single subject design, from studying treatments for rare patient populations to providing N-of-1 trial services in assisting physicians. The single subject design is an innovative addition to the arsenal of available methodologies for primary care physicians, biomedical students, residents, medical research faculty, clinical practitioners, among others. Consistent with the NIH Roadmap Initiative, increasing awareness of the utility in the single subject design could enhance treatment approach and evaluation both in biomedical research and primary care settings.

SSRD would require modification of the entrenched GD gold standard and, though the FDAAA expands the FDA's authority to demand more clinical research as a prerequisite for market approval, the legislation arguably is overwhelming, its effectiveness is subject to FDA enforcement, and it still has not been fully implemented

²⁰⁶ GROOPMAN, *supra* note 2, at 11-12.

²⁰⁷ JANOSKY, SINGLE SUBJECT, *supra* note 6, at 81. See also Malinowski & Gautreaux, *supra* note 16, *Drug Puberty?*, at nn. 187-190 and the accompanying text. Cf. Wylie Burke & Bruce M. Psaty, *Personalized Medicine in the Era of Genomics*, 298 JAMA 1682, 1682-84 (2007); Braff, *Patient-Tailored One*, *supra* note 13, at 9.

²⁰⁸ JANOSKY, SINGLE SUBJECT, *supra* note 6, at 95; *id.* at 82 ("Single subject study designs also provide greater flexibility for treatments, as ineffective interventions can be modified over the period of study. Thus, single subject designs should be considered when conducting research in biomedicine, as the methodology and interventions can be tailored for specific individuals.").

²⁰⁹ *Id.* at 28-29, 95; Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at 219-220.

²¹⁰ JANOSKY, SINGLE SUBJECT, *supra* note 6, at 28-29.

and subject to the potential court challenges that will arise.²¹¹ According to past experience and legal precedent, the means most likely to achieve a higher science standard for human clinical research are commercial incentives, direct government involvement in the research, or some combination of the two.

Commercial incentive-based programs to get desired clinical research done have proven effective and they have endured the threat of legal challenges. The most noted examples are the Orphan Drug Act (ODA) and the Best Pharmaceuticals for Children Act (BPCA).²¹² The FDA has successfully used ODA and BPCA to get needed clinical research done on small disease groups and children—research that industry avoided. ODA is a rewards-based program. The ODA methodology is to make drug development for small groups of patients commercially viable, and the mechanisms it employs are tax incentives, a seven-year period of market exclusivity, and other benefits.²¹³ ODA is working, and has been copied by other countries.²¹⁴

BPCA is legislation enacted to enable the FDA to get pediatric studies done and to recover from litigation challenging the FDA's attempt to force them.²¹⁵ The FDA introduced an incentive-based program—pediatric studies in exchange for six months of market exclusivity. When the FDA attempted to demand the studies for the same reward, litigation ensued and the FDA lost.²¹⁶ Congress stepped in to introduce an alternative: funding for the FDA through a trust to get pediatric studies done on its own and independent of commercial drug sponsors.²¹⁷ BPCA has worked to the extent that more pediatric studies are being done in spite of industry aversion to them.²¹⁸

The BPCA approach of the government directly funding needed research is an effective method for trumping legal challenges and moving science forward. The federal government has founded a new center to help cure the drug development dilemma by resurrecting drug development research abandoned by industry.²¹⁹ The center will be

²¹¹ See generally Evans, *Seven Pillars*, *supra* note 46; Evans, *New Infrastructural*, *supra* note 195.

²¹² Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107- 109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.), available at <http://bpca.nichd.nih.gov/>; *Orphan Drug Act*, Pub. L. No. 94-414 § 526(a)(2), 96 Stat. 2049 (1983, revised 2000), codified as amended at 21 U.S.C. §360bb (2000).

²¹³ *Orphan Drug Act*, Pub. L. No. 94-414 § 526(a)(2), 96 Stat. 2049 (1983, revised 2000), codified as amended at 21 U.S.C. §360bb (2000); Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 *IDEA*. 337 (2006).

²¹⁴ Some 350 orphan drugs have been approved in the U.S. market alone, and the program has been replicated by other countries. PhRMA, Pharmaceutical Researcher and Manufacturers of America. Office web site, available at http://www.phrma.org/profiles_and_reports (last visited June 9, 2010).

²¹⁵ Malinowski & Gautreaux, *Drug Puberty?*, *supra* note 16, at ___ (forthcoming).

²¹⁶ See, e.g., *Association of American Physicians and Surgeons Inc., et al, v. United States Food and Drug Administration*, 226 F.Supp.2d 204 (Oct. 17, 2002), 2002 WL 31323411 (D.D.C.).

²¹⁷ *Id.* at ___.

²¹⁸ Leslie Kushner, *Incentivizing Postmarketing Pharmaceutical Product Safety Testing With Extension of Exclusivity Periods*, 19 *FORDHAM INTELL. PROP. MEDIA & ENT. L.J.* 519, 546 (2009). See Rosemary Roberts, *FDA Perspective on FDAMA: Successes, Failures; Future Directions*, <http://www.fda.gov/cder/pediatric/presentation/FDAMA-FDA%20Persp-Roberts2004/sld008.htm> (last visited Oct. 30, 2008).

²¹⁹ See Harris, *New Federal Research Center*, *supra* note 164, at A1.

headed by Dr. Francis Collins, Director of the NIH and head of the U.S. Government effort to map the human genome, and its mission is to transition the accomplishment of the map of the human genome into human health applications.²²⁰ The scope of the center could and should be expanded to engage in clinical research with a SSRD component.²²¹ A major criticism of BPCA is the cost to taxpayers when the government directly engages in clinical research in conjunction with a new drug proposal.²²² However, the drug dilemma is costly—in terms of both human health and the U.S. economy. Investment in SSRD to turn the clinical trial gold standard into platinum would be justified given the enormous annual investment U.S. taxpayers make in biomedical research through NIH and other agencies, and the importance of the success of the U.S. biopharmaceutical R&D endeavor.²²³

B. UTILIZE FDAAA MECHANISMS

There are regulatory mechanisms in FDAAA that could effectively limit physician discretion to prescribe off-label and thereby push drug developers to achieve more during the premarket drug R&D process. Much depends upon how the FDAAA is implemented and enforced.²²⁴ First, the extra data generated under the FDAAA, both through expanded pre-market trials and Sentinel,²²⁵ would give the FDA the means to issue black box warnings and to demand notice of them through the dissemination component of Sentinel. The latter would affirm notice to physicians and potentially raise liability for ignoring black box warnings. The FDA has been utilizing the black box mechanism more frequently in recent years to reign in prescription pharmaceutical use, including off-label use.²²⁶ The black box—in literal terms, a black border around a written warning—is a visible sign that appears on package inserts for prescription drugs, which flags the danger of serious adverse events.²²⁷ These warnings, which the FDA may impose on rug labels or package inserts, flag that a drug carries significant risk of serious or even life-threatening adverse effects; it is the strongest warning the FDA may issue.²²⁸ The FDA is

²²⁰ *Id.*

²²¹ *Id.*

²²² See *infra* note 222 and accompanying text (cost of BPCA); ANGELL, TRUTH, *supra* note 7 (taxpayer investment in drug development).

²²³ See Malinowski, *Discourse*, *supra* note 20, at 13-19.

²²⁴ See generally Evans, *Seven Pillars*, *supra* note 46; Evans, *New Infrastructural*, *supra* note 195.

²²⁵ See generally Evans, *New Infrastructural*, *supra* note 195.

²²⁶ According to Professor O'Reilly, the FDA is requiring black box warnings earlier than prior to PDUFA legislation. JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 14:71 (3d ed., 2011), *citing* Testimony of Galson, FDA, to House Comm. on Govt. Reform (May 5, 2005).

²²⁷ See generally U.S. Food and Drug Administration, *Guidance for Industry. Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>. Retrieved 2010-02-21.

²²⁸ See Karen E. Lasser et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 JAMA 2215, 2216 (2002) (reporting that more than 10% of new chemical entities approved between 1975 and 1999 were given black-box warnings or withdrawn).

much more inclined to issue black box warnings on new drugs over older ones.²²⁹ A current estimate is that twenty percent of all drugs receive a black-box warning.²³⁰

Two other FDAAA mechanisms that could be employed to tailor existing off-label uses are the Risk Evaluation and Mitigation Strategy (REMS) and product cross-label provisions.²³¹ The FDAAA grants the FDA statutory authority to condition drug sales through REMS.²³² Through the FDA's cross-labeling authority under FDAAA, the FDA has authority to impose pharmacogenomics (new drug market access associated with genetic screening)—most notably given trends in the underlying drug development science, tie new drugs with associated genetic screens.²³³

Collectively, these mechanisms, with an information flow from Sentinel if that is successfully and meaningfully implemented,²³⁴ could check the 506(B) presumption in favor of market access with substantive knowledge about drugs on the market.²³⁵ Hopefully, pushed by Congress through the FDAAA, the FDA will accomplish more quality control.

C. CONDITION REIMBURSEMENT FOR OFF-LABEL USES

Drug development, as any other highly commercial endeavor, centers on market return—meaning physician-patient use and reimbursement. There are mechanisms in the established health care system to shift from traditional off-label use to use controlled by clinical data, but mounting health care finance pressures and ongoing reform, federal and state, open a door to a dimension of additional possibilities. There are pending legal and finance challenges to PPACA, but the legislation has been enacted, it is expansive (2,700+ pages) which suggests that at least some provisions will sustain legal challenges, and states do not have the luxury of waiting to see what happens with PPACA and are

²²⁹ Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225 n.114 (2011) (new drugs are overwhelmingly more likely than older drugs to be updated with black box warnings or other important safety information). *See also* Karen E. Lasser et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 JAMA 2215, 2215 (2002) (finding “half of [major changes to drug labeling] occurred within 7 years of drug introduction; half of the withdrawals occurred within 2 years”).

²³⁰ Evans, *Pillars*, *supra* note 46, at 429, citing Mei Sheng Duh et al., *The Role of Epidemiology in Drug Safety Litigations*, FOOD & DRUG L. INST. UPDATE, Nov./Dec. 2007, at 31, 31.

²³¹ Evans, *Pillars*, *supra* note 46, at 305, 511-512.

²³² *See* FDAAA § 901(b), 21 U.S.C.A. §§ 355-1(a)(1)-(2) (West Supp. 2009) (granting the FDA authority to require risk evaluation and mitigation strategies for drugs it puts on the market). The FDA has authority to restrict marketing and to require patient monitoring. 21 U.S.C.A. § 355-1(f)(3); *see also id.* § 901(a), 21 U.S.C.A. § 355(p) (West Supp. 2009) (making it unlawful for a person to introduce a new drug into interstate commerce if the drug requires a REMS and the person does not maintain compliance with the REMS); *id.* § 902(a), 21 U.S.C.A. § 352(y) (West Supp. 2009) (letting drugs be regarded as misbranded if manufacturers fail to comply with such restrictions). *See generally* Evans, *Pillars*, *supra* note 46, at 511-512.

²³³ *See generally* Evans, *Pillars*, *supra* note 46.

²³⁴ There are many variables to overcome, from cost to the proprietary nature of much of the information sought. *See generally* Evans, *Authority*, *supra* note 166.

²³⁵ *See supra* note 145 and accompanying text.

into the process of trying to comply—meaning that health care reform, federal and state, is underway.²³⁶

Under the established health care system, control over off-label use could be introduced through reimbursement restrictions under Medicare and Medicaid and the health insurance provided to federal employees. The pressures to cut health care costs are enormous—evident in the enactment of the PPACA.²³⁷ Editing reimbursement of off-label uses of pharmaceuticals makes sense on the levels of quality of care and cost savings. Industry should be pressured to engage in clinical research commensurate with actual clinical use and reimbursement. When an administration makes categorical changes regarding health care reimbursement for federal employees, the full portfolio of private health insurers servicing them adopts the policies and they make their way into the general public's policies as standard of care and coverage consistency.²³⁸

PPACA introduces two new mechanisms that could be implemented to directly curtail off-label uses of pharmaceuticals: the Center for Medicare and Medicaid Innovation to test new ways of delivering care to patients, and an Independent Payment Board²³⁹ to target waste in the system and recommend ways to reduce costs, improve health outcomes, and expand access to high quality care.²⁴⁰ The IPAB—slated to consist of fifteen experts, including doctors and patient advocates nominated by the President and confirmed by the senate—is a backstop that will take effect only if Medicare costs grow too fast.²⁴¹ However, trends suggest that is inevitable.²⁴² IPAB will make recommendations to Congress to promote cost and quality of care, which Congress may accept or reject.²⁴³ If Congress opts to reject and Medicare spending surpasses specific targets (which it likely will based upon current trends),²⁴⁴ it must enact policies that achieve equivalent savings or let the Secretary of Health and Human Services follow IPAB's recommendations. The IPAB is a wonderful opportunity to check physician off-label use of pharmaceuticals in the absence of supportive clinical data and to promote SSRD.

²³⁶ Catherine Kitchen, Presentation, Health Law Survey, LSU Law Center (April 2011) (Ms. Kitchen is Director of Policy, Department of Health and Hospitals, and directly working on LA compliance with PPACA).

²³⁷ See *supra* notes 71-72 and accompanying text.

²³⁸ Author's experience handling reimbursement matters for biopharmaceutical and medical device companies while in private practice.

²³⁹ The White House Blog, The Facts About the Independent Payment Advisory Board, Apr. 20, 2011, available at <http://www.whitehouse.gov/blog/2011/04/20/facts-about-independent-payment-advisory-board>.

²⁴⁰ Visit the Internet site of the government's initiative at <http://www.healthcare.gov/> (last visited July 27, 2011).

²⁴¹ *Id.*

²⁴² See generally PWC REPORT, *supra* note 5.

²⁴³ Visit the Internet site of the government's initiative at <http://www.healthcare.gov/>. IPAB is specifically prohibited by law from recommending any policies that ration care, raise taxes, increase premiums or cost-sharing, restrict benefits or modify who is eligible for Medicare. *Id.*

²⁴⁴ See generally PWC REPORT, *supra* note 5.

The PPACA also establishes an Innovation Center authorized to test innovative care and payment models.²⁴⁵ Congress created the Innovation Center under the Affordable Care Act, giving the Center the authority and direction to “test innovative payment and service delivery models to reduce program expenditures, while preserving or enhancing the quality of care”²⁴⁶ for those who get Medicare, Medicaid or Children’s Health Insurance Program (CHIP) benefits. Congress funded the Center with \$10 billion for 2011 through 2019. The goal is to raise the quality and value of care, which is in sync with the law-policy proposals put forth in this article to edit physician discretion to use pharmaceuticals outside the scope of the data that puts them on the market and raise the science standard for new drug approval.

V. CONCLUSION

Testimony before Congress about the unreliability of prescription drugs, like testimony over the birth control pill in 1972, triggered significant law-policy change, sweeping FDAAA legislation—though the recent testimony failed to capture the same public attention.²⁴⁷ Unfortunately, the FDAAA does not break cleanly from the legacy of excessive physician discretion to prescribe pharmaceuticals off label, meaning prescribing drugs beyond the scope of FDA market approvals and the data that puts drugs on the market.²⁴⁸ Traditional off-label discretion, a hold-over from the middle of the last century, draws drug developers into investing resources in marketing rather than clinical research²⁴⁹ and invites physicians to experiment on their patients well outside the scope of research standards, including regulations to protect human subjects.²⁵⁰

A major premise of this article is that the broad off-label usage norms are antiquated—a reflection of the crude science past in pharmaceutical R&D and paternalism in the practice of medicine, which are not consistent with the present consumer-driven era in medicine and contemporary genetics. This article proposes utilizing existing mechanisms and implementing the FDAAA to limit physician off-label discretion through a heightened regulatory standard for introducing pharmaceuticals to patients in need of care. Patients, like the physicians writing their prescriptions, are engaged in clinical care, not clinical research, and when subjected to prescriptions off-label are drawn outside the scope of the clinical data putting drugs on pharmacy shelves and regulations to protect human subjects. Today’s Dr. Marcus Welby should take fewer liberties and demand more data.

²⁴⁵ For information about the Innovation Center, visit the official Internet site at <http://innovations.cms.gov/> (last visited July 30, 2011).

²⁴⁶ *See id.*

²⁴⁷ *See supra* notes 1-2 and accompanying text. *See generally* Evans, *Seven Pillars*, *supra* note 46; Evans, *Authority*, *supra* note 166.

²⁴⁸ *See supra* notes 169-173 and accompanying text.

²⁴⁹ ANGELL, TRUTH, *supra* note 7, at 135-172.

²⁵⁰ *See supra* note 55 and accompanying text.