

I N T R O D U C T I O N

The Gatekeeper

REGULATION AND LAW currently put American citizens at second remove from therapeutic medicines. In order to use most drugs, citizens must obtain a prescription from a licensed and qualified medical authority, usually a physician. Yet before anyone can prescribe, the U.S. Food and Drug Administration must approve. No new drug can be legally marketed in the United States unless the Administration has explicitly declared it “safe and effective” for its intended uses. This authority renders the FDA the gatekeeper of the American pharmaceutical marketplace, and it sustains a battery of vast powers. Among these are the power to define medical success and shape scientific careers, the power to limit advertising and product claims, the power to govern drug manufacturing, the power to enable drug firms to generate vast riches and the power to chase those same firms from the marketplace, the power to sculpt medical and scientific concepts, and ultimately the power to influence the lives and deaths of citizens. Some of those citizens may be harmed from hazardous or ineffective therapies that the FDA has approved. Other citizens may suffer or die waiting for the agency to approve a potentially effective cure. Still others, perhaps most, may easily use a drug whose dosage, label, and chemical form have been carefully honed through the scrutiny that regulation brings. Whatever the outcome, the FDA has shaped the lives of one and all. Among the thousands of people who daily give painstaking attention to the agency’s every utterance and movement, there is considerable disagreement about the Food and Drug Administration—it is venerated in one corner and bemoaned in another; it is targeted for expansion by one voice, for evisceration by a second—but there is no serious doubt about its reach or significance.

The Administration’s formal powers engender a broader and more opaque set of informal forces. From one vantage, the agency’s formal authority is limited to the jurisdictions and territories of the United States. It legally tends the boundaries of only one nation. From another vantage, however, the FDA rules the entire global pharmaceutical market. The United States is among the world’s wealthiest nations and its pharmaceutical market is, at this time, by far the world’s largest. And it has exploded in recent decades; the American market accounted for \$216 billion in spending on prescription drugs in 2006, more than five times the \$40.3 billion spent in 1990. At this writing, furthermore, the United States is the only major world economy without explicit pharmaceutical price controls through national health insurance. Because admission to the U.S. market is the preeminent site of profit for the world’s drug companies, the FDA’s veto power over entry into the American health-care system translates into global economic and scientific reach. Be-

yond this, the Administration carries a stature that other agencies in foreign nations consciously emulate or resist. Pharmaceutical regulators in Australia, Brazil, Egypt, France, Germany, Great Britain, India, Israel, Japan, South Korea, Switzerland, and dozens of other countries and regions model themselves upon the FDA, and in some cases contrast themselves against it.¹

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The public has been given to believe that the Food and Drug Administration is, of its nature, a social good.

—*Wall Street Journal* editorial, 1987

Americans are justifiably proud of the regulatory system set up by the government to test new drugs... Most consumers in this country are satisfied to rely on the FDA's time-consuming evaluations, because when that agency finally approves a drug, it is almost certainly both safe and effective.

—*Washington Post* editorial, 1989

The regulatory power of the FDA became irrefutably clear in the spring and summer of 1987. Those months marked a dire, contentious moment in the industrial history of biotechnology. On the last Friday in May, an FDA advisory panel took the apparently benign step of requesting “additional data” for a drug called Activase. Activase is the trade name for a protein called tissue plasminogen activator, or TPA. At first glance, there was nothing particularly odd or daunting about the committee's request. The advisory boards counseling the FDA routinely ask for more information about the drugs they are vetting.

In the annals of American history, however, tissue plasminogen activator would qualify as something more than an ordinary drug. TPA is not a traditional “small molecule” like those that had dominated therapeutics for gen-

¹As shorthand for the Food and Drug Administration I refer to “the Administration,” its formal title and its referent in much correspondence over the past seven decades. In doing so, I follow U.S. statutes and legal practice. When discussing a particular presidential regime (the “Nixon administration,” or the set of bureaucratic and executive appointees who served from January 1969 to August 1974), I will make the reference clear. Prescription drug spending aggregates appear in Kaiser Family Foundation, “Prescription Drug Trends” (Menlo Park, CA: Kaiser Family Foundation, September 2008).

erations. Tissue plasminogen activator is a biologically active protein found in the cells lining blood vessels; it is a “large molecule” much more complex than traditional drugs of the twentieth century. More importantly, in 1987, researchers understood that intravenous administration of TPA could dissolve clots much more quickly and with less risk of hemorrhage than previous anti-clotting drugs. Activase would thus carry the potential for treating numerous diseases in which blood clots play a role, including stroke and heart attack. With its novel mechanism of action and its potentially vast market, TPA promised “to be the first blockbuster drug in the biotechnology industry,” according to the *Washington Post*. TPA was developed by the darling of the new biotech sector, Genentech, based in South San Francisco, California. A “blockbuster” is drug industry parlance for a highly lucrative drug, generally one that generates \$1 billion per year or more in revenues. By reaping vast profits, a blockbuster drug like Activase can pay off hundreds of other, less fortunate wagers that a drug company has made upon promising but never-marketed therapies.²

In the spring of 1987, for many investors, all bets literally were off. The panel’s decision on Friday, May 29, was a refusal to recommend licensing of Activase, and it presaged a more drastic event; on June 15, the Administration would reject the drug for marketing in the United States. The panel’s vote on May 29 was announced after stock markets had closed. When stocks opened for trading on Monday, June 1, Genentech’s share price quickly plunged by \$11.50, to \$36.75. In an instant, \$928 million—nearly a quarter of the publicly traded value of the biotechnology industry’s star company—had vanished.

American financial markets were not the only audience stunned by the FDA committee’s data request and the agency’s rejection of Activase. The *Wall Street Journal* editorial page—which has long positioned itself as a

²Examples of small molecules include penicillin, lovastatin (Mevacor, the first “statin” for high cholesterol), or even fluoxetine (Prozac, the first selective-serotonin reuptake inhibitor for depression). TPA is often expressed as tPa or tPA in the scientific literature, and is also known as alteplase. According to the *Boston Globe*, TPA would qualify as “the fledgling [biotech] industry’s first major drug” (“Genentech Setback is Only Good News for Competitors,” June 16, 1987). TPA also had the benefit of “fibrin specificity,” in that its activity was focused on clot-bound plasminogen and it promised to lower induced bleeding in the brain that was associated with many anti-coagulant drugs. For a reasonably accessible introduction, consult Wolfram Bode and Martin Renatus, “Tissue-type plasminogen activator: variants and crystal/solution structures demarcate structural determinants of function,” *Current Opinion in Structural Biology* 7 (6) (Dec. 1997): 865–72; Richard W. Smalling, “Molecular Biology of Plasminogen Activators: What Are the Clinical Implications of Drug Design?” *American Journal of Cardiology* 78 (12A) (Dec. 19, 1996): 1–7.

On the biotechnology industry of the time, see Louis Galambos and Jeffrey Sturchio, “Pharmaceutical Firms and the Transition to Biotechnology: A Study in Strategic Innovation,” *Business History Review* 72 (2) (Summer 1998): 256–60; Walter W. Powell, “The Social Construction of an Organizational Field: The Case of Biotechnology,” *International Journal of Biotechnology* 1 (1) (1999): 42–67. On Genentech in particular, consult Robert Teitelman, *Gene Dreams: Wall Street, Academia, and the Rise of Biotechnology* (New York: Basic Books, 1989).

pro-business, libertarian critic of the FDA—called the advisory panel the “flat earth committee.” Yet the *Journal’s* most severe criticism was reserved not for the committee but for the agency it served, “the FDA bureaucracy.” In a particularly shrill essay entitled “Human Sacrifice,” the *Journal’s* editorial page argued:

Patients will die who would have lived longer. Medical research has allowed statistics to become the supreme judge of its inventions. The FDA, in particular its bureau of drugs under Robert Temple, has driven that system to its absurd extreme. The system now serves itself first and people later. Data supercede the dying. . . .

We will put it bluntly: Are American doctors going to let people die to satisfy the bureau of drugs’ chi-square studies?

The *Journal’s* editorialists were perhaps the most strident of the FDA’s detractors that year, but they were not alone. The *Washington Post* ran an article entitled “TPA Foot-Dragging Costs 30 Lives a Day.” Daniel Koshland, editor of the journal *Science*, wrote bluntly, “When a circus clown steps on his toes and falls on his face, it is a cause for laughter. When a regulatory agency that licenses drugs for heart attacks stumbles, it may have not only egg on its face but blood on its hands.” Respected cardiologists at the National Institutes of Health, Washington University in St. Louis, Harvard Medical School, and the University of Michigan also openly disparaged the panel. Other critics pointed to France and New Zealand, among other countries, where the drug was being approved or was already launched.³

Like other laments about the TPA case, the *Journal* editorial targeted not a single decision but an entire regulatory structure. Why were potentially life-saving drugs being held up to the standard of narrow statistical tests and elaborately designed trials? Why was a single government agency—and not the wider and decentralized community of medical practice, or the drug marketplace—positioned as the arbiter of a drug’s efficacy? To the *Journal* and many other concerned observers, modern medicine’s overreliance on statistics to judge drug effectiveness was mainly the fault of the FDA. For conservative critics of American pharmaceutical regulation, quantification and bureaucracy ran together in a patient-killing, market-thwarting, unholy alliance.

³Andrew Pollack, “FDA to Get More Data on Key Genentech Drug,” *NYT*, May 26, 1987. Marilyn Chase, “FDA Panel Rejection of Anti-Clot Drug Sets Genentech Back Months, Perils Stock,” *WSJ*, June 1, 1987, 26. “The Flat Earth Committee,” *WSJ*, July 13, 1987, 22. Marjorie Sun, “Heart Drug in Limbo: FDA Panel’s Decision on TPA, an Eagerly Awaited Clot Dissolver, Stuns Doctors and Wall Street,” *WP*, July 28, 1987, H7; “Human Sacrifice,” *WSJ*, June 2, 1987, 30; “TPA Foot-Dragging Costs 30 Lives a Day,” *WP*, Nov. 3, 1987. Daniel E. Koshland, Jr., “TPA and PDQ,” *Science* 287 (July 24, 1987): 4813. For an early power-based interpretation of this controversy, see Usher Fleising, “Risk and Culture in Biotechnology,” *Trends in Biotechnology* 7 (3) (March 1989): 52–7. Critics included cardiologists Eugene Braunwald (then chairman of the department of medicine at Harvard Medical School) and Eric Topol (then at the University of Michigan); two decades later, Topol would emerge as a strident drug industry critic and defender of FDA safety standards.

Matters were more complicated and uncertain than the *Journal's* diatribe would suggest. At the core of the TPA controversy were some complex issues of causation, human pathology, and drug design. The advisory panel agreed with Genentech's claims that TPA dissolved clots, but said that there was little evidence directly tying the drug to improved survival among heart attack victims. The panel basically agreed with an FDA statistician's lament that Genentech had failed to conduct studies showing a clear and direct human benefit from the drug. The dispute over TPA's effectiveness connected to a broader debate about the value of "surrogate" markers and endpoints—variables like tumor reduction, viral load, cholesterol statistics, and clot formation that were correlated with mortality, but only partially and often misleadingly. There was also evidence—sufficiently noteworthy to cause anxiety among some financial analysts as well as FDA officials—that Genentech's proposed dose for TPA was too high, leading to bleeding in the brain. Some critics charged that the Administration had changed standards and reviewing panels midway through the approval process, a shift that was in part a reflection of TPA's odd status at the intersection of traditional drugs and biologically active proteins.⁴

So, too, did the FDA show itself to be more flexible than its detractors judged. Just five months after the panel's request for more information, TPA was licensed for marketing in the United States, based upon results from two new trials that showed a more direct link between the drug's clot-dissolving activity and improved health outcomes. At the time of product licensing, one FDA official quipped that "we are all glad that it's going to get on the market and off our backs." Just as surely as the agency's conservative and libertarian critics had piled laments upon its delay, now other critics began to wonder whether TPA had been ushered into the market too quickly and whether the drug had been overhyped. The drug's approval was seen by many critics as highly problematic, not least because TPA sold for ten times the dose price of streptokinase, the drug it aimed to replace. *Time* magazine published an article entitled "Cheaper Can Be Better" in March 1991, in which TPA's relative benefits were criticized. Sidney Wolfe, a physician with

⁴By contrast, the same advisory panel approved intravenous use of streptokinase for post-heart attack administration on May 29, in part because the streptokinase application was accompanied by a controlled study with over 11,000 patients that used mortality as the measured endpoint. An extensive contemporary account of these developments appears in Maggie Mahar, "The Genentech Mystique: How Much Science? How Much Hype?" *Barron's* (Jan. 11, 1988). Walter W. Powell offers an especially insightful narrative in "The Social Construction of an Organizational Field," 53–9. For other treatments, consult Baruch A. Brody, *Ethical Issues in Drug Testing, Approval and Pricing: The Clot-Dissolving Drugs* (New York: Oxford University Press, 1995); and Charles Mather, Usher Fleising, and Liam Taylor, "Translating Knowledge from Bench to Bedside: The Controversial Social Life of t-PA," *Risk Management: An International Journal* 6 (2) (2004): 49–60. Toshihiro Nishiguchi (*Managing Product Development* (New York: Oxford University Press, 1996), 240–55) and Philip Hilts (*Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Knopf, 2003, 300–303) also offer able and engaging summaries of the scientific (and political) issues at stake.

Ralph Nader's interest group Public Citizen, argued that the flood of new and highly expensive but marginally more effective drugs was a wider problem—only 30 percent of new drugs were truly innovative, he argued—of which TPA was a poster child. TPA's success in reducing bleeding problems in the brain and other organs did not materialize. While some trials showed benefit from the drug, a series of studies published from 1989 through the early 1990s failed to find a significant aggregate difference in effectiveness and safety between TPA and streptokinase.⁵

The saga of tissue plasminogen activator is significant not merely as medical history, but as a canvas in which the politics of pharmaceutical regulation and government power are illuminated. A subtle request for information had derailed an entire industry's hopes, had erased millions of dollars in investment value, and had set in motion a wide-ranging controversy to which major national newspapers were devoting prime news and editorial pages. None of this import was lost on Genentech's executive at the time, G. Kirk Raab. Raab was hired specifically to smooth the company's journey through the regulatory process. Years later, Raab would describe regulatory approval for his products as the fundamental challenge facing his company. And he would depict the Administration in a particularly vivid metaphor.

I've told a story hundreds of times to help people understand the FDA. When I was in Brazil I worked on the Amazon River for many months selling Terramycin for Pfizer. I hadn't seen my family for eight or nine months. They were flying in to Sao Paulo, and I was flying down from some little village on the Amazon to Manous and then to Sao Paulo. I was a young guy in his twenties. I couldn't wait to see the kids. One of them was a year-old baby, the other was three. I missed my wife.

There was a quonset hut in front of just a little dirt strip with a single engine plane to fly me to Manous. I roll up and there is a Brazilian soldier standing there. The military revolution had happened literally the week before. So this soldier is standing there with this machine gun and he said to me: "You can't come in." I was speaking pretty good Portuguese by that time. I said: "My god, my plane, my family, I gotta come in!" He said again: "You can't come in." I said: "I gotta come

⁵The remark of the unidentified FDA official appears in Michael Specter, "FDA to Approve New Drug for Heart Attacks," *WP*, November 13, 1987, A16. Andrew Purvis, "Cheaper Can Be Better," *TIME*, March 18, 1991. Cardiologist Richard Smalling would summarize that "t-PA failed to lessen the risk of bleeding complications that had plagued the use of streptokinase"; Smalling, "Molecular Biology of Plasminogen Activators," 2. On the international study concluding that streptokinase had the optimal risk-benefit profile—led by Peter Sleight of Oxford and Charles H. Hennekens of Harvard Medical School—see Kathy Fackelmann, "Sizing Up the Risks of Heart-Saving Drugs," *Science News*, March 9, 1991. The International Study Group, "Mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase with or without heparin," *Lancet* 336 (1990): 71–5. Reviews of "drugs" and "biologics" were bundled into one center—the Center for Drugs and Biologics—in 1987, but criticism from the TPA case may have led the FDA to split biologics from drug review; Marilyn Chase, "FDA Will Split Up Its New Drug Unit in an Attempt to Streamline Procedures," *WSJ*, Oct. 2, 1987, 24.

in!” And he took his machine gun, took the safety off, and pointed it at me, and said: “You can’t come in.” And I said: “Oh, now I got it. I can’t go in there.”

And that’s the way I always describe the FDA. The FDA is standing there with a machine gun against the pharmaceutical industry, so you better be their friend rather than their enemy. They are the boss. If you’re a pharmaceutical firm, they own you body and soul.⁶

Raab’s account, taken from an oral history, waxes hyperbolic and jumbles images. The FDA is possessor (“owner body and soul”) of a company, its superior (“boss”), and in the most jarring image, a gun-toting soldier. The FDA’s gatekeeping power over the pharmaceutical marketplace was the reason that Raab told his allegory “hundreds of times.” Like the Brazilian soldier keeping Kirk Raab from a flight to see his family, the FDA as gatekeeper separates would-be entrants from the space they wish to inhabit: the American pharmaceutical market. Even if Raab inflated the FDA’s power, his exaggeration was common in industry circles at the time. Claims like Raab’s, moreover, perpetuated the FDA’s power in reputation by overstating it. In practice, dealing with the fact of FDA power meant a fundamental change in corporate structure and culture. At Abbott and at Genentech, Raab’s most central transformation was in creating a culture of acquiescence toward a government agency. As was done at other drug companies in the late twentieth century, Raab essentially fired officials at Abbott who were insufficiently compliant with the FDA.⁷

In the context of the TPA controversy, Kirk Raab’s reminiscences are telling in two other ways. First, his casual use of multiple metaphors—ownership, hierarchy, gatekeeping, gun-pointing—gestured to the many powers that he perceived in the agency’s regulatory arsenal. The power of the FDA was not limited to gatekeeping alone. One of these powers, as Raab recognized, was the power to shape standards of scientific evidence and the concepts defining them. TPA received regulatory approval only after Genentech submitted trials showing a change in heart function, beyond the dissolution of blood clots. What counted as a “cure” in the treatment of heart attacks would be defined not only by a broad community of cardiologists, but also (and perhaps primarily) by an organization of government scientists and regulators.⁸

⁶G. Kirk Raab, “CEO at Genentech, 1990–1995,” an oral history conducted in 2002 by Glenn E. Bugos, Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2003, 11–12. Genentech’s market value dropped by \$928 million in response to the FDA panel’s decision, but a number of other biotech stocks plunged as well; “Genentech, Biotechnology Stocks Tumble After Ruling on TPA Drug for Blood Clots,” *WSJ*, June 2, 1987, 3.

⁷A similar development occurred at Cetus corporation in 1990, when CEO Robert Fildes resigned under pressure from shareholders and directors after taking an antagonistic stance toward the FDA; Marilyn Chase, “Fildes Quits Top Cetus Jobs in Wake of FDA’s Rebuff,” *WSJ*, Aug. 17, 1990, B1. Raab remarks, “I changed the culture at Abbott to friendliness, to seeking advice, and working with the FDA”; Raab, “CEO at Genentech, 1990–1995,” 12.

⁸Marilyn Chase and Joe Davidson, “FDA to Clear Genentech Drug for Blood Clots,” *WSJ*, Nov. 13, 1987, 42. Of course, the FDA’s definitions of curing are not independent of those in

Second, there was praise in addition to fear. In closing his discussion of the all-powerful agency, Raab extolled the very regulators who stood between his company and the marketplace. Along with its formidable status, the agency was also depicted as competent and benevolent, with a kind of compassion and service clearly impossible for the Brazilian soldier of his memory.

I should make something very clear. There are a lot of very dedicated, capable people [who] do very important work at the FDA. Sometimes I may not agree with them or think they take too long, but I know their ultimate goal is to improve public health in the United States.⁹

This facet of the FDA's reputation clearly bothered *Wall Street Journal* editorial writers in the 1980s. Their criticism of the agency did not meet with wide agreement or public reception. The FDA was generally and broadly admired among American citizens; the deep linkage between the agency's power and its reputation was, to the *Journal* editors, a stubborn fact that needed to be challenged. "The public has been given to believe that the Food and Drug Administration is, of its nature, a social good," the editorialists observed. Two years later, in the midst of the AIDS crisis and its challenge to modern medicine and government policy, the *Washington Post's* editorial writers noticed a similar pattern. "Americans are justifiably proud" of their system of pharmaceutical regulation, the *Post* editorial stated. Reminding readers of how, just a quarter-century before, the FDA rescued Americans from a European drug tragedy, the *Post* editorial made a bold statement about the medical and social confidence inspired by FDA regulation, as "when that agency finally approves a drug, it is almost certainly both safe and effective."¹⁰

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The chronicle of tissue plasminogen activator leaves puzzles that beg for explanation and inquiry.¹¹ How is it that in the United States, long known as the land of weak regulation, smaller government, and powerful business,

communities of cardiology, and the advisory committee system can be seen as a set of networks that link a regulatory organization to various professional audiences for information and legitimacy; see chapters 5 and 7.

⁹Raab, "CEO at Genentech, 1990–1995," 11–12.

¹⁰"Drugs for the Dying," *WP*, July 11, 1989, A24. The *Journal* and other critics called for "a national debate," a re-education of the public and the national media in which the agency's image would be recast from protector to bottleneck; "TPA: Tip of the Iceberg," *WSJ*, Dec. 2, 1987, 28. It was for this reason, perhaps, that the *Journal* criticized Robert Temple, even though the agency's scientific star had not been involved in the FDA's decision on Genentech. The journal could criticize Temple, but in regulatory and scientific circles his judgment was considered rigorous and credible.

¹¹What follows is a suggestive list only; I recast some of these puzzles below in the section "The Scope and Variance of Regulatory Power: Some Comparative and Historical Riddles," and in the particular analyses of the following chapters.

a regulatory agency—*any* regulatory agency—could “own you body and soul”? How could a government agency literally reshape the content and method of scientific research? How could such an agency exercise such vast sway over sectors—including financial markets and the industry of research and development—that it did not directly govern?

How in the United States—a society characterized by the distrust of government power, and at no time more starkly than in the 1980s during the presidency of Ronald Reagan—could a federal regulatory agency have an enviable public reputation that commentators on the left and right duly recognized? How could such a reputation endure through criticism by scientists, by corporations, by major newspapers? Perhaps more important, how could an agency inspire admiration from society while also being feared by some of its most powerful members?

Other puzzles are more particular to the TPA case but gesture to broader dynamics and patterns that have eluded clarity. How could a prominent drug be approved quickly in France—the exemplar of an activist regulatory state in democratic societies, and one with stringent price controls upon its drug market—but not in the United States? Why during the 1980s did the FDA clear AIDS drugs so much more quickly than it cleared TPA, which treats a disease that killed many more Americans at the time?

Finally, how did TPA’s sponsor, Genentech, survive, see its child to approval and marketing, and further prosper as one of the preeminent scientific corporations of our age? How did other companies and drugs avoid TPA’s fate and pass through the regulatory process smoothly? Why did thousands of other drugs (and companies sponsoring them) fail and disappear from public memory?

REPUTATION AND THE PUZZLES OF REGULATORY POWER

In a nation as purportedly anti-bureaucratic as the United States, the FDA’s power in the national health system, in the scientific world and in the therapeutic marketplace is odd and telling. It is odd because the ability of an established business firm to develop and market a new product is essentially subject to veto by a federal regulatory agency. It is telling, I think, because the accretion and use of this gatekeeping power encompass a politics of reputation that suffuses numerous agencies of state—regulatory, military, security-oriented, policing, welfare—yet is rarely recognized.

The puzzle is one of economic regulation and government power. While other agencies of government have the authority to regulate a product or a firm *after* it has set foot in the marketplace—the ability to constrain a product’s price, to remove large quantities from circulation by seizure, to compel factories to reduce pollution, to issue monetary fines to companies large and small—the Administration has the authority to restrict products from entering a market in the first place. Among the agencies that possess this power—

state licensors, permitting agencies—few if any have the discretion, authority, and conceptual influence of the FDA. The difference between pre-market (*ex ante*) and post-market (*ex post*) regulatory power is crucial. With fewer resources than most other government agencies, the FDA can leverage its veto authority into much greater sway over the pharmaceutical marketplace, global clinical research, multimillion-dollar advertising and sales campaigns, everyday medical practice, and other realms of the modern world.

This puzzle of power has defied the two most prominent accounts of regulation: public interest and capture theories. The rise and operation of regulatory power in American pharmaceuticals does not reflect the self-protecting initiative of drug companies in the United States. While drug companies have exercised considerable influence in the policy process and on the FDA, they have generally resisted the accrual of regulatory power to the FDA, contrary to what capture explanations suggest. When deregulatory or business-friendly measures have come to American pharmaceutical regulation, they have arrived more at the behest of scientific organizations, consumer activists, and organized patient groups than at the order of drug companies themselves. FDA regulatory decisions have not, moreover, consistently favored the largest and most powerful firms in the industry, as capture theory predicts. When patterns of industrial advantage are observed, they are generated much more by the politics of reputation than by the politics of capture.¹²

Nor does the power of American government in pharmaceutical regulation stand as a simple reflection of a democratic “popular will” or a straightforward response to a “market failure.” While the FDA’s power in pharmaceutical regulation has depended heavily upon broad popular support for its governing role, numerous facets of that power—authority over drug production and medical research, conceptual influence in science, and the many uses of gatekeeping—were shaped much more by regulatory officials themselves. The empowering agent for FDA behavior has been less the public or a fictional “median voter” aware of the failings of therapeutic markets than a networked congeries of audiences—pivotal professional and scientific networks, congressional committees, consumer representatives, and media organizations.

Reputation—understood as a set of symbolic beliefs about an organization, beliefs embedded in multiple audiences—comprises the central response of this study to the puzzle of American regulatory power in the global pharmaceutical world. Reputation built regulatory power in all of its facets. And power, once possessed, has been used and managed in ways that maintain reputation, and hence power itself. Power is also deployed, of course, to

¹²I discuss these two theoretical approaches at greater length in chapter 1. At various points in the succeeding chapters, I provide abundant evidence against modified capture accounts, such as the claim that scientific organizations and patient groups were merely doing the bidding of drug companies in the twentieth century, and thus the companies’ control was all the more effective because it was indirect. Some have claimed that the past ten years provide evidence of a more captured agency, especially in pharmaceutical policy; I examine this claim in chapter 12.

advance the public health aims that animate many of the agency's members. Yet these aspirations have not arisen independently of organizational image, and the very notions of public health and public good that motivate so many federal officials have been shaped in the politics of reputation.¹³

The regulatory power of the Food and Drug Administration stems in large measure from a reputation that inspires praise and fear. Various facets of that reputation were on display in the TPA controversy—metaphors of vigilant gatekeepers, exacting FDA scientists like Robert Temple who demanded statistical rigor in new drug development, the thalidomide tragedy and the actions of Administration officials (especially medical officer Frances Kelsey) who kept it from the U.S. market, public opinion polls and journalistic writings that imparted vague but no less powerful faith to the agency and its operations. One facet of the Administration's reputation appears in its warm public image as a protector of patients and consumer safety. Another, related facet of the agency's image comes in its reputation for scientific accuracy. These positive faces of the agency's reputation have not held uniformly. As the TPA saga suggests, the FDA has been subject to withering and persistent criticism from many quarters—political, scientific, medical, and economic—over the past half-century. Indeed, the FDA's reputation for citizen protection has waned in recent years, having faded in a way that casts much of the past half-century in stark relief. Yet over the past seventy years, as the *Wall Street Journal* and *Washington Post* editorial pages both recognized in the 1980s, the FDA has generally received praise for its pharmaceutical governance from broad and often surprising quarters. Perhaps most telling, politicians, firms, doctors, and organized interests have consistently tried to use the FDA's "protector" reputation as a rhetorical tool to advance their policy objectives. In so doing, they unconsciously testify to the reputation's stability, and they reproduce its basic symbols and beliefs.¹⁴

If the FDA's reputation has been tarnished in recent years, this fact yields a conundrum of its own. It is puzzling politically and historically that, in the late twentieth-century United States, a federal agency could have a reputation good enough to smudge. The idea that a government organization has lost credibility presupposes, in some sense, that it possessed meaningful credibility to begin with. Except for particular periods whose exceptional nature proves the rule, national political culture in the United States has often been hostile to the idea that government agencies are to be trusted.¹⁵

¹³I offer a more extended definition of reputation and elaborate upon its operation in chapter 1.

¹⁴I discuss recent damage to the agency's reputation in chapter 12, "A Reputation in Relief." Narratives of criticisms from numerous quarters and distributed through manifold networks appear in chapters 3 through 6.

¹⁵For general reviews of the anti-administrative strain in American political culture, consult Richard Hofstadter, *Anti-Intellectualism in American Life* (New York: Knopf, 1963), chapters 7, 8, and 15; Stephen Skowronek, *Building a New American State: The Construction of National Administrative Capacities, 1877–1920* (New York: Cambridge University Press, 1982), chapters 1–5; Daniel Carpenter, *The Forging of Bureaucratic Autonomy: Reputations, Networks*

In its regulation of pharmaceuticals, the U.S. Food and Drug Administration marks an important exception to this pattern. In the 1970s, as public opinion on government capacity soured, the FDA and its regulatory work regularly received 70 to 80 percent or more “approval” or “confidence” from citizens surveyed; this was double or more the confidence ascribed to the federal government, to Congress and various presidents of the time in the same surveys. In the middle of the 1990s, at a time when national surveys showed that public trust of the federal government in general had fallen to about one-quarter of the American public, and that there was tepid support even for national space programs, the federal government’s operations in food and drug regulation still attracted “a great deal of support” from six in ten survey respondents. In several such analyses, no other federal government agency or function scored as high as the FDA. In numerous other surveys taken over the past half-century, the FDA has consistently been named or identified as one of the most popular and well-respected agencies in government. This pattern cannot be explained by the hypothesis that Americans are ignorant of what the agency does. Aggregate survey data also suggest that Americans’ familiarity with the FDA is at or near the highest among federal government agencies.¹⁶

Statistical data from public opinion surveys, particularly those that attempt to measure something as emotion-laden (and perhaps unconscious) as confidence in a federal agency, must be interpreted with great caution. Trust in a particular government organization can be easily conflated with norma-

and Policy Innovation in Executive Agencies, 1862–1928 (Princeton: Princeton University Press, 2001), introduction, chap. 2, and chap. 10.

¹⁶The American National Election Studies (ANES) has since 1952 asked questions about American citizens’ “trust in government.” The high point of the ANES index came in 1966, when 61 percent of respondents favorably answered the question: “How much of the time do you think you can trust the government in Washington to do what is right— just about always, most of the time or only some of the time?” The low point for the past half-century came in 1994, when the relevant figure had fallen to 26 percent.

In 1995 and 1997, pollsters Peter D. Hart and Robert M. Teeter and their research firms conducted two surveys for the Council for Excellence in Government, asking approximately 1,000 American adult citizens about their support for government programs. More than half of respondents expressed “strong support” for the programs identified as “Social Security” (69 percent), “The armed services” (64 percent), “Enforcing food and drug safety regulations” (60 percent), and “Enforcing environmental protection laws” (55 percent). Perhaps surprisingly, some traditionally popular functions received low marks, including “NASA and the space program” (34 percent) and “Federal law enforcement, such as the FBI,” 45 percent; Council for Excellence in Government, *Attitudes Toward Government—February 1997* (Washington, DC: Council for Excellence in Government, 1997).

Another Hart-Teeter survey taken in 1999 reported that when respondents were asked to think about whether and how a particular program benefits them, 58 percent of respondents replied that “food and drug regulation” benefited them “a great deal” or “a fair amount.” This aggregate outranked the statistic for “public universities” (50%) “consumer safety regulation” (56%), “medical research” (48%), “Medicare” (38%), “Environmental laws and regulations” (50%), and “Social Security” (42%). Indeed, in this survey no other federal government

tive beliefs about which policy functions of government are legitimate or desirable. Quite possibly, survey respondents will express support for the FDA because they believe that the federal government ought to be involved in protecting the nation's supply of food and drugs, even if they think that the government did a mediocre job at its task. Or perhaps survey respondents think not about the agency generally but about their own experience with product safety; if their experience has been a safe one, they might credit the agency even if the agency deserves no such tribute. Even if these limitations can be overcome, it is simply very difficult to measure the concept of trust, credibility, and legitimacy with surveys. Aggregate public opinion data are nonetheless suggestive in two senses. First, the Administration consistently ranks appreciably higher than many other agencies, including those whose policies seem to be broadly supported. Second, the data cohere with the assessments of journalists, medical journal editors, and others about the long-running public trust in the FDA.¹⁷

Some of the most persuasive evidence about the FDA's reputation comes from the rough and tumble of American politics, where conservatives and liberals alike heap praise upon the agency in making arguments for their favored policies. In the decades-long debate over the affordability of brand-name prescription drugs, one idea that has been consistently floated in recent years is that of "re-importing" drugs from Canada and other foreign nations where the national health system constrains drug prices. In opposing this initiative, conservative politicians and policy advocates have pointed

function performed as high; only local government functions such as "roads" (70%) and "public schools" (65%) were rated higher. *America Unplugged: Citizens and Their Government* (Washington, Council for Excellence in Government, 1999), 14–15.

Former FDA general counsel Peter Barton Hutt cites statistics showing that FDA's "public confidence rating" was 80 percent in the 1970s, 61 percent in 2000, then declined to 36 percent in 2006; Peter Barton Hutt, "The State of Science at the FDA," *Administrative Law Review* 60 (Spring 2008), 443, citing William Hubbard and Steven Grossman, "Presentation to the FDA Alumni Association" (Apr. 11, 2007), slide 7 (in Hutt's possession). Fran Hawthorne (a senior contributing editor of the finance monthly *Institutional Investor*) remarks that "poll after poll has always shown" the FDA to be "one of the most trusted arms of the entire government"; *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat* (New York: Wiley, 2005), viii.

In 2003 and 2004, the FDA had the highest recognition among federal agencies among survey respondents who answered the following question: "I will read you a list of federal government agencies. Please say for each if you understand what it is and does, or not." 98 and 97 percent of survey respondents answered the question affirmatively for the FDA, respectively, in 2003 and 2004. "CDC, FAA, NIH, FDA, FBI and USDA Get the Highest Ratings of Thirteen Federal Government Agencies," *PRNewswire*, Feb. 6, 2007, table 1.

¹⁷On methodological issues affecting "trust in government" studies, consult Jack Citrin, "Comment: The Political Relevance of Trust in Government," *APSR* 68(3) (Sept. 1974): 973–88; Joseph S. Nye, Philip D. Zelikow, and David C. King, *Why People Don't Trust Government* (Cambridge: Harvard University Press, 1997), particularly essays by Derek Bok, Jane Mansbridge, David King, and the introductory essay by Nye; Steven Van de Walle and Geert Bouckaert, "Public Service Performance and Trust in Government: The Problem of Causality," *International Journal of Public Administration* 26(8, 9) (Jan. 2003): 891–913.

more to the purportedly weaker safety standards—“Canadian drugs are not FDA-approved”—than to the possible ill effects of price regulation.¹⁸

In a different way, liberal politicians have seized upon the agency’s history of regulating drugs before their market introduction to propose a similar system for the regulation of tobacco products, especially cigarettes. Until June 2009, when President Barack Obama signed the Family Smoking Prevention and Tobacco Control Act, these efforts were unsuccessful, not least because of intransigent opposition from some tobacco companies, and in part because a March 2000 Supreme Court decision issued the unanimous opinion that Congress consciously excluded the regulation of tobacco products from the FDA’s regulatory mandate. When in 1992 Commissioner of Food and Drugs David Kessler claimed authority to regulate the cigarette as a medical device, he and his allies in the effort were not so much trying to reclassify tobacco as to bring the product under broadly legitimated mechanisms of American governance and health: the FDA’s gatekeeping power over new therapies. The oddity of this scheme is that there are many other agencies that could, in theory, regulate cigarettes, including the Federal Trade Commission, the Treasury Department (the Bureau of Alcohol, Tobacco and Firearms), and the U.S. Department of Agriculture. American reformers and politicians gestured to the FDA’s drug approval system as a regulatory model, and in June 2009, they established that model in law.¹⁹

When politicians appeal to an agency’s reputation, their invocation does not itself establish the organization’s credibility. Yet in making arguments about how FDA pre-market judgments about drugs ought to be extended in their authority (to foreign products) or to new products (cigarettes), politicians are relying upon what they suppose that others believe. The others in question may be voters, or jurors and judges, or state and local elected officials, or physicians or pharmacists; in national politics, the important criterion is that they are numerous. Similarly, in their claim that re-importing drugs from an immediately neighboring, advanced industrial nation (one to which Americans travel by the tens of millions every year) courts health hazards, conservative politicians and other officials are relying upon public

¹⁸For a review of the claims and arguments surrounding drug safety and re-importation, see Marv Shepherd, “Drug Importation and Safety of Drugs Obtained from Canada,” *Annals of Pharmacotherapy* 41 (7) (2007): 1288–91. Some of the claims made about the lower safety profile of drugs approved by the Canadian government were made by FDA leaders themselves, particularly Bush administration appointees. The aggregate effect of these claims was probably to weaken the agency’s credibility; Marc Kaufman, “FDA: Canadian Drug Position Misinterpreted,” *WP*, May 26, 2003, A11; Patricia Barry, “States Defy FDA on Drug Importation,” *AARP Bulletin*, Oct. 2004.

¹⁹Kessler recounts the episode in his book, *A Question of Intent: A Great American Battle with a Deadly Industry* (New York: Public Affairs Press, 2002); Allan Brandt, *The Cigarette Century: the Rise, Fall and Deadly Persistence of the Product that Defined America* (New York: Basic Books, 2007), 391–97. Hawthorne, *Inside the FDA*, 58–60. Martha Derthick, *Up in Smoke: From Legislation to Litigation in Tobacco Politics*, 2nd ed. (Washington, DC: Congressional Quarterly Press, 2004), chapters 1, 4, and 8. The Court’s decision came in *FDA v. Brown and Williamson Tobacco Corp.*, 529 U.S. 120 (2000); see chapter 12.

believes that the FDA is a uniquely protective institution. These appeals to the protective ability of the FDA may be insincere. Yet in the high-stakes world of pharmaceutical politics, such rhetorical appeals must be credible to be worth repeating. American politicians rarely point favorably to federal regulatory agencies other than the FDA, moreover, in their arguments for or against particular policies.²⁰

The tougher surface of the FDA's protective image—the diligence of a policing regulator in constraining and at times punishing the behavior of those private entities that break basic rules of society, science, and the marketplace—is one that many citizens admire and expect. The fearsome side of the agency's reputation also appears more vividly to particular audiences in business and medicine. It emerges in the agency's capacity to dash the hopes and the expected earnings of drug sponsors, to negate tens or hundreds of millions of dollars of investment, many thousands of hours of research, and entire careers spent in the development of a new therapy. At times, the fearsome side of reputation enacts a form of power itself, as the agency relies upon different facets of its ambiguous but dreaded image to induce agreeable patterns of behavior by pharmaceutical companies, by physicians and clinical researchers, and by other regulatory agencies worldwide.

REGULATORY POWER: DIRECTIVE, GATEKEEPING, AND CONCEPTUAL

The enigma of American pharmaceutical regulation lies in the power that a national bureaucratic organization exercises over the discoverers, producers, prescribers, testers, sellers, and consumers of prescription drugs. This power is manifold; there is no one scepter that contains all of the regulatory power of the FDA. In representing regulatory power in the modern pharmaceutical world, I have chosen a threefold conception that harkens to an older tradition of inquiry in political science and sociology. The idea is that power exists not only in broad formal authority to direct the behavior of others (directive power) but also in appearances that are less obvious: the ability to define what sorts of problems, debates, and agendas structure human activity (gatekeeping power), and the ability to shape the content and structure of human cognition itself (conceptual power).²¹

²⁰The methodology of inference from repeated statements that may be insincere or even false is taken from Walter Johnson's insightful study of the stock narratives repeated in lawsuits over slave sales in the antebellum slave market of New Orleans. Johnson, *Soul by Soul: Life inside the Antebellum Slave Market* (Cambridge: Harvard University Press, 1999), 12.

²¹I offer a more extended definition and discussion in the following chapter. The notion of different faces of power owes its origins to studies of Peter Bachrach, Morton Baratz, Robert Dahl, John Gaventa, and Stephen Lukes, among many others. Regulatory power is different from community power, from economic power, and from the sort of domination implied in studies of class power. My adoption of the terminology of directive, gatekeeping, and conceptual power is meant to differentiate between the kind of power that I and others see in the FDA and the kind of power that these analysts see in community elites, in organized business interests, or in the capitalist class.

All three of these faces of regulatory power appear in the Administration's regulation of therapeutic products. Directive power rests in the Administration's ability to command the various subjects of regulation—pharmaceutical and biotechnology companies; medical researchers; and pharmacies, clinics, and other stores that sell drugs. The agency is endowed by federal statute with the capacity to seize pharmaceutical products that misbranded or are otherwise deemed in violation of the law. FDA officials can order pharmaceutical makers to insert documents to their product packaging, to add or subtract language to advertisements and labels, and to alter their chemical synthesis and manufacturing processes. The Administration writes substantive regulations governing the manufacture, development, testing, submission, and marketing of pharmaceutical products, and these regulations generally carry the full force of federal law. When companies violate these regulations or the statutes on which they are based, the agency can refer cases to the U.S. Department of Justice for criminal prosecution.

The gatekeeping facet of regulatory power becomes visible only upon closer inspection of the regulatory process. It is the narrowing of decisions and deliberations to many fewer drugs (and fewer issues about drugs) than might occur if institutions were different. One reason that the drug development process does not generate more controversy in the United States is that many questionable and marginal drugs are never submitted or developed. Out of fear of rejection or stringency at the FDA, sponsors abandon hundreds if not thousands of new therapeutic ideas every year. These hard cases never appear before the Administration, and so its officials need not deal with the contentious issues they involve. The very "agenda" of drugs developed and submitted to the Administration (and numerous other drug regulatory agencies around the world) is shaped by anticipation and fear of the Administration's likely response. To be clear, this pattern is not necessarily regrettable; federal regulation prevents and deters many sub-par and unsafe therapies from entering the American health-care system.

The gatekeeping power of the Administration in the American pharmaceutical marketplace stems from its ability to veto product entry, combined with the fact that FDA approval is the only route to market for a new drug. Beyond this, the Administration's drug review decisions—to confer or not to confer rights to a sponsor to market a new drug—are, for all intents and purposes, uncontestable. Over the past half-century, if Administration officials declared a new drug "not approvable," there was little that any company or scientist could do, without great cost and low probability of success, to overturn or circumvent this decision.

From another vantage, the Administration's historical emphasis upon pre-market regulation serves to conceal many issues surrounding the safety of marketed drugs. This suppression of issues and information does not flow from a bureaucratic conspiracy of any sort, but from the way that the Administration's powers are defined and limited. So too, the definition of pharmaceutical politics in terms of "safety and "efficacy" excludes other impor-

tant questions from discussion—the heterogeneity of individual responses to drug treatment, the therapeutic experience of millions of human subjects in ongoing clinical trials, the continued operation of placebo effects in markets for prescription pharmaceuticals, and the therapeutic implications of drug advertising and labeling.

A conceptual facet of regulatory power rests more quietly, but not less forcefully, in the capacity to shape patterns and terms of thought and learning. It is fair to say that the basic terms, standards, schedules, and rules of modern drug development have been fashioned by the Administration as much as by any other global entity. When scientists and physicians test a new drug in clinical studies separated by “Phase 1,” “Phase 2,” and “Phase 3”; when companies submit a study “protocol” to the Administration that defines hypotheses and measures before their assessment and use; when firms and physicians debate the “efficacy” and “safety” of a drug before its approval or afterward; when scientists attempt to demonstrate the “bio-availability” of a drug in a given dosage form; when legislators write laws and insurers write policies governing generic drugs that depend upon demonstrations of “bioequivalence”—in these cases and many, many others, human agents are consciously and unconsciously using terms that have been deeply and thoroughly shaped by officials of the Food and Drug Administration. In making this point, I do not claim that the Administration “invented” these terms, or that FDA officials were the only agents involved in shaping them. The narratives that follow reveal the roles of other agents in the evolution of the concepts and structures of the modern pharmaceutical world. Yet they also reveal that scientific and technical considerations have rarely if ever operated independently of national regulation in the formation of therapeutic concepts.

In the American governance of pharmaceuticals, as in other realms of political activity, organizational reputation supports regulatory power in its directive, gatekeeping, and conceptual faces. Directive power—especially legal and statutory authority—depends upon the conscious and repeated deference of legislators, judges, executive branch officials, state-level regulators, and physicians and scientists to endow the Administration with authority over the therapeutic marketplace. These decisions and nondecisions (the often unseen choices not to contest the FDA’s power or its exercise) depend in large measure upon the Administration’s legitimacy: its scientific esteem, its history of consumer protection, its occasionally fearsome practices of enforcement, its expressions and demonstrations of benign purpose. Gatekeeping power rests upon reputation as well. The constant monitoring of the FDA by physicians, scientists, drug companies, investors, journalists, and others testifies to the demand for information on its officials’ intentions. The Administration’s reputation for exacting scrutiny of new drug applications and experimental plans induces thorough documentation, caution in development, and often the wholesale discarding of new therapies. In other ways, as I hope to show, this reputation encourages a certain kind of risk-

taking, leading some scientists and firms to pour much more into the experimentation and science than they otherwise would have. Regulatory power of the conceptual kind, too, is supported and shaped by reputation. The Administration is perceived as authoritative on those matters where its definitions carry sway, and in many other cases the power of the FDA has become so routine in its exercise that it is no longer meaningfully contested in law, science, or national politics.

Power does not equate to domination. Firms, professional organizations, and other actors in the modern pharmaceutical world also carry power, and they use it constantly. Moreover, the reputation-based power of any organization rests in the judgment of its audiences; those audiences have a form of power, too, as their assessments may diminish if the organization's behavior exhibits a lack of propriety, equanimity, or honesty. In the modern pharmaceutical world, medical organizations and pharmaceutical companies are both represented by vaunted and well-heeled lobbies. These lobbies have been skilled at cultivating and creating allies among large investors, organized patient advocates, universities and think tanks, and newspaper and medical journal editors. Consumer safety advocates have fewer resources and professional clout than do drug companies and organized physicians, but they enjoy widespread media access and coverage. FDA officials occasionally and properly express fear of the political clout of companies and professions—the occasional suggestion or bill or campaign to reduce the Administration's authorities or to subject the agency to greater oversight or constrain its operations. The Administration's leaders also worry about how a medical study or a new report by one of the agency's watchdogs will generate embarrassment, legislative and scientific scrutiny, emboldened challenges from the agency's subjects, and perhaps reduced authority. At some level, then, the modern pharmaceutical world involves many ongoing contests of power.

This plurality of contests does not, however, imply a pure balance of force. Over the late twentieth century, few regulatory agencies of any sort, in any nation, possessed or exercised the power held by the Food and Drug Administration. The breadth and depth of the Administration's power become clearer when its different faces are examined, and when other institutions of regulation are compared to it. The authority of the FDA to affirm and deny entry to the pharmaceutical market was innovative and, more important, globally influential in the twentieth century. Compared to other countries, particularly European regulatory regimes for drugs in the 1960s through 1990s, the United States housed much more regulatory power in its national food and drug agency. Few regulators in the United States or other countries possess such broad power to deter companies from investing in certain ideas or developing new products. Fewer still are those regulatory agencies whose concepts and structures of thought have created entire new industries and have fundamentally refashioned scientific disciplines. Even as political, economic, and scientific influence have shifted toward the organized pharma-

ceutical industry in recent decades, hundreds of pharmaceutical firms still take implicit and explicit orders from FDA officials on matters both minute and grand.²²

There is nothing false or mythical about the relationship between power and reputation. To say that reputation upholds a government agency's power is not to say that power is ill-founded, unconstitutional, or illegitimate. Quite the opposite, I would argue. In a democratic republic where ultimate sovereignty rests with the people and their collective will, one might think that a government agency should have a reputation characterized by trust and expertise.

So too, to argue that the Food and Drug Administration has power is not to say that it is too powerful, or that it is necessarily more powerful than the industries and companies it regulates. I am rather interested in other questions: whether the FDA is more or less powerful over the course of time; whether the Administration bears more power vis-à-vis regulated firms, compared to other national agencies that govern the same companies. I am interested in the Administration's power compared to what it might have been, under plausibly and slightly different circumstances. The statements about power advanced in this book are historical. They are comparative across nations and organizations. They are at times counterfactual.

THE SCOPE AND VARIANCE OF REGULATORY POWER: SOME COMPARATIVE AND HISTORICAL RIDDLES

An intensive study of one government agency may seem of limited value for understanding other organizations. Is a focused assay of American pharmaceutical regulation over seven decades a "case study" of an organization whose patterns illustrate those of other agencies, and if so, why not examine

²²The contest of power is continual, so much so that the often hackneyed point about power being "essentially contested" is a truism in regulatory affairs. We see hints of such notions of "essential contest" in postmodern and conservative writings alike about the state. As Michael Oakeshott argued in his Harvard lectures, governance occurs in spheres well outside the apparatus of the state. "Governing is an activity which is apt to appear whenever men are associated together or even whenever, in the course of their activities, they habitually cross one another's paths. Families, clubs, factories, commercial enterprises, schools, universities, professional associations, committees, and robber gangs may each be the occasion of this activity. And the same is true even of gatherings of persons (such as public meetings), so long as they are not merely ephemeral or fortuitous. Indeed, it may be said that no durable association of human beings is possible in the absence of this activity"; *Morality and Politics in Modern Europe: The Harvard Lectures* (New Haven: Yale University Press, 1993), 8. Quoted in William Novak, "The American Law of Association: The Legal-Political Construction of Civil Society," *Studies in American Political Development* 15 (Fall 2001): 164, n.6. For French philosopher Michel Foucault's concept, see "Governmentality," in Graham Burchell, Colin Gordon, and Peter Miller, eds., *The Foucault Effect: Studies in Governmentality* (Chicago: University of Chicago Press, 1991), 87–104. Foucault's and Oakeshott's points (and general principles) are quite different, of course, yet they both recognize the breadth of governance outside of state realms.

these other cases as co-equal recipients of attention? Or is the FDA so unique that its analysis speaks with limited range to other settings? I think neither of these concerns has warrant. The main problem comes with the term “case study” and its all too casual use in academic work. To call something a “case study” assumes the goal of extracting universal knowledge about a population from a singular entity. A study thus amounts to a “case” only when its characteristics are representative of those shared by a larger population of research objects; a pharmaceutical regulator in the United States could, under this reasoning, represent all other pharmaceutical regulators, all other government agencies, or even all other organizations. The problems here are at least threefold. First, one might question the existence of a larger population sufficiently homogenous in so many respects that we would care to generalize about it. Is the U.S. Civil War really a “case” of a population of other “civil wars”? Many contemporary scholars assume this much in their quantitative studies of a generic phenomenon called “civil war.” Yet thousands of students and scholars have examined that bloody conflict not as a “case” of a larger category, but because its occurrence more or less visibly changed so many other things in the United States and elsewhere, for decades, maybe more than a century afterward. Second, there is value in studying a singular process not because it stands in for so many others, but because it differs so radically and starkly from others, so much so that the act of comparison is itself problematic. To call a nation an “outlier” or an extreme in the path of economic development or political institutions does nothing to explain how it achieved such a distinctive place. Indeed, the assignment of “outlier” status to distinctive phenomena in the social sciences amounts to a partial or total forfeiture of the information that can be learned from these entities. A narrative may be so distinctive as to gesture to broader dynamics by casting the difference of almost all other cases in such stark relief, thereby illuminating what is normal about them.

Finally, there is value in studying a singular process not because it stands in for so many others, but because it influences so many others. The national histories of England, France, and Spain in modern global history come to mind. A narrative carries more weight when the “case” in question has become not a sample from a larger population, but indeed a model by which those other cases have evolved or have been generated. Inclusion of these phenomena in a comparative or statistical analysis—the simplistic application of John Stuart Mill’s “method of comparison” to such entities—in fact commits immense errors of inference, as the independence assumptions so central to modern social science comparisons are violated when one case becomes a reputational benchmark or attractor for others.²³

²³Historian of physics Peter Galison has rendered the point with hilarity: “Imagine a book entitled *A Case Study in European History: France*. This made-up title strikes me as immensely funny, not because it purports to be a detailed study of an individual country (there are many important national histories), but because it encourages the reader to imagine a homogeneous class of European countries of which France is an instance. The absurdity rests upon the dis-

More generally, my analysis of the FDA's power and reputation is undertaken in comparison—at times explicit, at times implicit—with regulators in other settings. When these comparator institutions are viewed, it becomes clear that the U.S. Food and Drug Administration requires some historical and theoretical reckoning. On any number of dimensions, the FDA differs materially, sometimes radically, from foreign drug regulators. Perhaps the most important dimension lies in the early evolution and massive scope of FDA power. Governments worldwide now require regulatory approval of drugs before marketing, but a nationally centralized, fully administrative process of new drug review, based upon government evaluation of data from phased clinical trials, came first in the United States. The FDA has long employed more scientists and more heavily trained personnel than other agencies performing its functions, at times (in the 1970s) more so than in all the world's other drug regulators combined. Even as agencies in Europe and Asia have advanced in recent years, the United States still houses the strongest of global pharmaceutical regulators.²⁴

- Why in the United States—the reputed “weak state” of the Western world, the government of what De Tocqueville, Hegel, and Marx all observed as a near “stateless” society,²⁵ the home of big business and small government, and the bastion of laissez-faire economic policy—has the national government displayed the world's most far-reaching and stringent regulations on medicines? Why, for most of the twentieth century, has the FDA exercised a greater degree of formal power and informal discretion over drug development and marketing than have other national regulators?

The second and more enduring puzzle comes not from difference but from similarity. Where cross-national similarities appear, they often derive from institutional mimicry. When pharmaceutical regulation in Australia, Brazil, China, Great Britain, India, Japan, New Zealand, South Korea, and Switzerland looks like pharmaceutical regulation in the United States, it is in

crepancy between the central and distinctive position we accord France in history and the generic position we must assume France occupies if we wish to treat it as a ‘case’; Galison, *Image and Logic: A Material Culture of Microphysics* (Chicago: University of Chicago Press, 1997), 59. For the most influential treatment of non-quantitative research in the framework of a linear regression model, see Gary King, Robert Keohane, and Sidney Verba, *Designing Social Inquiry: Scientific Inference in Qualitative Research* (Princeton: Princeton University Press, 1994). I have profitably drawn upon King, Keohane, and Verba's model in previous work, but the limits of rendering narrative research as a “qualitative regression” have become more apparent to me as I have analyzed and pondered the world of global pharmaceutical regulation. The present study stands, I hope, as an example of the value of focusing on a distinctive organization and narrative whose “independence” from other organizations cannot be maintained, even conditionally.

²⁴See chapter 11 for evidence of this point.

²⁵On the consensual view of the United States in the nineteenth century as a “weak state,” see Skowronek, *Building a New American State*, chapters 1 and 2. For a critical review, see William Novak, “The Myth of the ‘Weak’ American State,” *American Historical Review* 113 (2008): 752–72.

large measure because these nations have borrowed heavily from the U.S. example. The ubiquity of national pre-market review for medicines as a global phenomenon is not intrinsic to pharmaceuticals but instead postdates the FDA's powers. Among the nations regulating pharmaceutical approval, moreover, none has been more influential than the Administration in setting standards of clinical trials, drug evaluation, approval criteria, and surveillance of drugs on the market. This strong state presence in pharmaceutical regulation developed and persisted even as the United States was much less active in other realms of domestic policy: government welfare programs, the provision of social insurance and health insurance, and the regulation of occupational health and safety, agriculture, and environment. With global and national reach, the Food and Drug Administration is sometimes regarded as “the world's most powerful regulatory agency,” an assessment that refers to American pharmaceutical regulation as much as any other facet of the agency.²⁶

In the latter half of the twentieth century, an American model for pharmaceutical regulation has been perhaps the primary institutional export of the United States (see table I.1). It is fair to say that no other sector of global regulation—certainly not environmental or labor regulation, but also regulatory regimes in telecommunications, energy, transportation, antitrust, finance, and consumer product safety—has witnessed so great an emulation of U.S. organizational structures, procedures, and standards as has the realm of global pharmaceuticals. Nor can this pattern be chalked up to industrial dominance. American pharmaceutical companies did not dominate global drug innovation until after the period (the 1950s through the 1980s) when U.S. drug regulation became a formal and informal international standard. The regulatory dominance of the FDA in pharmaceutical regulation, in other words, is disproportionate to the scientific leadership and the economic leadership of the United States. Countries such as the United Kingdom, Germany, France, and Japan—all of them global industrial leaders in the late twentieth century, and all of them with more extensive welfare states

²⁶Norway and Sweden preceded the United States in establishing legal pre-market regulation of drugs, and in law Sweden had an efficacy requirement for the registration of new drugs in 1935. Yet it was in the United States where a fully administrative new drug process was created (from 1938 to the 1950s), and the institutions and protocols of drug efficacy developed in the 1950s and 1960s FDA were pivotal in the subsequent development of regulatory standards throughout Europe and (through the WHO) globally. Hence, pharmaceutical regulation stands as a partial contrast to comparative portraits of the state in which the United States appears laggard, weak, or exceptional in its reliance on private mechanisms. Paul Pierson, *Dismantling the Welfare State? Reagan, Thatcher and the Politics of Retrenchment* (Cambridge: Cambridge University Press, 1994); Jacob Hacker, *The Divided Welfare State* (New York: Cambridge University Press, 2002); Monica Prasad, *The Politics of Free Markets: The Rise of Neoliberal Economic Policies in Britain, France, Germany and the United States* (Chicago: University of Chicago Press, 2006). See the judgment of Hilts, *Protecting America's Health*: “Because of its influence outside of the United States, [the FDA] has also been described as the most important regulatory agency in the world” (xiv).

TABLE I.1
Features of U.S. Pharmaceutical Regulation Adopted in Other Nations

Standardized New Drug Application (NDA) and NDA Review Process	Regulated R&D Process (Phased Studies) and Protocol Requirements	Bioequivalence and Bioavailability Regulation	Good Manufacturing Practices	Guidelines for Clinical Evaluation
Evolved 1938–1955, NDA form federally published 1955	Investigational New Drug (IND) Regulations, 1963	First regulations, 1970; final regulations, 1978	Regulations in 1956	First distributed 1971
Later adopted in: <ul style="list-style-type: none"> • (W.) Germany (1961) • Japan (1962) • European Economic Community (EEC) directive, 1965 • France (1967, 1978): [Déclaration d'Auto- risation de Mise sur le Marché (AMM)] • Britain (1971) • China (1985) • Australia (1989/1990) 	Later adopted worldwide, including: <ul style="list-style-type: none"> • Britain (1963) • European Economic Community (EEC) (1975) • Netherlands (1975) • Norway (1975) • Sweden (1975) • (W.) Germany (1978) • Australia (1989/1990) • China (1999) 	Later adopted worldwide, including: <ul style="list-style-type: none"> • EEC and Europe (1983) • World Health Organization (WHO) directive (1975) • Australia (1990) 	Later adopted worldwide, including: <ul style="list-style-type: none"> • Japan (1975) • European Economic Community (EEC) (1975) • Australia (1991) • WHO (1975) • Sweden (1975) 	Later adopted worldwide, including: <ul style="list-style-type: none"> • Britain (1974, 1977) • European Economic Community (EEC) (1975) • Japan (1992) • China (1999)

Note: For sources, and other practices and standards that have diffused worldwide, including the notion of a centralized regulatory agency for foods and drugs, the concept and method of surrogate endpoints in clinical trials, and Good Laboratory Practices, see chapter 11.

than in the United States—have been laggard adopters of pharmaceutical standards when compared to the FDA.

- Why until recently has the realm of global pharmaceutical regulation been characterized by such vast emulation of the American model? Why is it that, while national regulatory policies in the realms of finance, labor safety, and environmental regulation have converged upon international governance regimes or partially voluntary standards (such as the International Standards Organization—ISO), drug regulation programs worldwide have converged upon government agencies with pre-market approval powers? Why, in other words, is there less variation across nations and regions in pharmaceutical regulation than we might expect, and why is the American model of regulation copied in the realm of pharmaceuticals when no such American model enjoys popularity or supremacy in other areas of regulation (environmental, health and safety, labor, financial, etc.)?

An additional puzzle emerges less from the comparison of the FDA to other national pharmaceutical regulators, but from comparing the Administration to other regulatory agencies within the United States.

- Why is it that, within the United States, the agency responsible for pharmaceutical regulation exercises more forceful and more discretionary powers than do national agencies regulating other sectors of the national economy?

American regulation of financial and securities markets is nearly a century old, but no national agency has meaningful discretion to review and approve each and every financial instrument or debt issue before its appearance, or to approve an industrial product before its marketing.²⁷ The Federal Trade Commission has governed standards of trade and the practices of advertising since 1913, but nothing in federal statute or practice permits the FTC to review and potentially veto advertisements before they appear. Since 1970, the Occupational Safety and Health Administration (OSHA) of the federal government has inspected hundreds of thousands of workplaces nationwide, while the National Highway Transportation Safety Authority (NHTSA) has responsibility for auto safety. But nothing in federal statute or regulatory practice requires businesses to receive federal approval from OSHA before starting work or production, and no federal agency is empowered to unilaterally halt the development of new automobiles before their market introduction. Like so many forms of national regulation in the United States, regulation of workplace safety and automobile safety occurs mainly after a business has already started and after a car has been produced and marketed.²⁸

Even where U.S. regulatory agencies have some official veto power over

²⁷Indeed, during the New Deal, the very years in which the FDA acquired its pre-market review power, the United States rejected industrial licensure. Relevant provisions of the National Industrial Recovery Act (NIRA) were voided in *A.L.A. Schechter Poultry Corp. v. United States*, 295 U.S. 495 (1935). This is not to deny the very expansive nature of the New Deal experiment; Edwin Amenta, *Bold Relief: Institutional Politics and the Origins of Modern American Social Policy* (Princeton: Princeton University Press, 1998); Jennifer Klein, *For All These Rights: Business, Labor, and the Shaping of America's Public-Private Welfare State* (Princeton: Princeton University Press, 2004). The more enduring legacy of New Deal institution-building lay in a more robust antitrust regime; Ellis Hawley, *The New Deal and the Problem of Monopoly* (Princeton: Princeton University Press, 1966).

Not coincidentally, in their analysis of regulation, economic theorists have focused almost entirely on institutions of price and quality regulation, neglecting the set of institutions that regulate R&D and/or that confer marketing rights before price and quality are shaped in a market equilibrium. See Jean-Jacques Laffont and Jean Tirole, *A Theory of Incentives in Procurement and Regulation* (Cambridge: MIT Press, 1994); this interesting book and its accompanying mathematical literature shed little if any light on institutions of pharmaceutical regulation, health and safety regulation, consumer products regulation, and occupational safety regulation.

²⁸The most relevant form of federal regulation of automobiles before their market introduction comes in the Corporate Average Fuel Economy (CAFE) standards, which are loosely en-

market entry by firms—as when they must issue licenses or permits for construction, grazing, development on wetlands, or other rights to economic activity—they rarely have the power to define the parameters of product development, research, and experimentation and production. Before its demise in 1995, the Interstate Commerce Commission (ICC) regulated railroad prices for freight and passengers, railway safety, and interstate freight transport by trucks. While the ICC had licensing authority over firms, it did not directly govern the development of new transportation technologies, and it did not exercise primary force in standardization of the railroads. In the United States, federal regulation over telecommunications has been conducted by the Federal Communications Commission since 1934. While the FCC assigned and governed broadcast license rights for most of the twentieth century, its powers were circumscribed, particularly in comparison with telecommunications regulators in European countries.²⁹

Another puzzle concerns federalism. Among three critical nations with domestic pharmaceutical industries and national regulatory agencies—Australia, China, and India—a more decentralized, federalist mode of regulation is observed. Such a federalist mode is also observed in the European Union, which still permits country-by-country drug approval through its “decentralized procedure.” The existence of regional and subnational regulators in other countries demonstrates that there is nothing natural or inevitable about national-level pharmaceutical regulation.

- Why is pharmaceutical regulation nationalized in the United States, while other forms of regulation are not? Put equivalently, why is pharmaceutical regulation nationalized in the United States when other nations, most notably Australia and India, have had more decentralized, regional agencies that regulate medicines?

Some final puzzles concern the FDA itself.

- Why has the FDA enjoyed greater discretion, policymaking authority, and deference from other branches of government in its regulation of drugs, compared to its regulation of foods?
- What accounts for some of the intricate and counterintuitive patterns of interplay between firms, scientists, federal regulators, and social groups in the United States? And how does this most powerful agency exercise its power with such limited resources?

forced and which affect only the average fuel economy for a fleet. See more generally Jerry L. Mashaw and David L. Harfst, *The Struggle for Auto Safety* (Cambridge: Harvard University Press, 1990).

²⁹On transportation regulation, consult Ari Hoogenboom and Olive Hoogenboom, *A History of the ICC: From Panacea to Palliative* (New York: Norton, 1976); Lawrence Rothenberg, *Regulation, Organizations and Politics: Motor Freight Policy at the Interstate Commerce Commission* (Ann Arbor: University of Michigan Press, 1994). For a clear and accessible discussion of wetland permitting, see Brandice Canes-Wrone, “The Influence of Congress and

NARRATIVE, COMPARISON, AND STATISTICS:
EMPIRICAL APPROACHES OF THIS STUDY

The world of pharmaceuticals and their regulation is a vast and complex one. I have written this book with the intent to preserve much of that complexity while giving readers a conceptual frame in which the history and some enduring patterns of political economy can be understood and rethought. My goals will have been met if the book leaves readers with an appreciation for the historical and political complications of U.S. pharmaceutical regulation as well as some general lenses through which the seemingly familiar can be viewed in a different, potentially surprising, and illuminating way.

The intensive empirical approach of this study stems not only from the complexity and ubiquity of the subject matter but from its theoretical inspiration to examine reputation. Analysis of an agency's reputation requires analysis of its audiences. Where the projections of an organization meet its audiences, where symbols engage their viewers and texts encounter their readers—this is the space inhabited by organizational image. As a reputation consists of symbolic beliefs embedded in various overlapping audiences, the study of an organizational reputation must investigate both the various symbols that represent the organization and the structure of that organization's relationships to different audiences. Both the content and the consumers of a reputation—and most vitally the nexus between them—merit systematic and enduring study.

Another reason for preserving and presenting the complexity of U.S. pharmaceutical regulation is that most attempts at simplification—and there have been many—have been misleading. There are dozens of writings on U.S. pharmaceutical regulation, and there are many, many more on prescription drugs and the American and global pharmaceutical industries. Those efforts, while collectively fascinating and occasionally enriching, often portray an all too simple landscape. In one common narrative, a government agency protects millions of citizens from unscrupulous businesses whose lust for profit vastly outweighs their concern for public health or consumer safety. In another account, much more popular in recent years, the agency has been taken over by the very companies it is supposed to govern, converted to a servant of industry. In other stories, an overzealous and illegiti-

the Courts over the Bureaucracy: An Analysis of Wetlands Policy,” in Scott Adler and John Lapinski, eds., *The Macropolitics of Congress* (Princeton: Princeton University Press, 2006). On the American regulation of telecommunications, consult James L. Baughman, *Television's Guardians: The FCC and the Politics of Programming, 1958–1967* (Knoxville: University of Tennessee Press, 1985); Barry Cole and Mal Oettinger, *The Reluctant Regulator: The FCC and the Broadcast Audience* (Boston: Addison Wesley, 1978). Shalini Venturelli, *Liberalizing the European Media: Politics, Regulation and the Public Sphere* (Oxford: Oxford University Press, 1998).

mate government regulator, subservient either to populist, anti-technology consumer advocates or to drug companies themselves, deprives patients of medicines that would save their lives, and suffocates the innovative technology coming from one of modern capitalism's most dynamic sectors.³⁰

At different moments, each of these narratives tells a partial truth. Cautious bureaucrats have bungled. Profit-thirsty firms have recklessly produced and poorly tested unsafe drugs that have killed and maimed. Pharmaceutical firms have indeed exercised more sway over regulatory affairs in recent decades. Yet in the aggregate, and over the course of decades of American and global history, these stories fundamentally mislead. More compelling and accurate truths lie not merely in between these extremes, but on other dimensions of experience. Ignoring these dimensions, these narratives divert our attention from the ongoing politics of experimentation and therapy, from the small but crucial battles over interpretation of data, over the meaning of a patient's heart attack or stroke, over the design of a medical experiment, over the image of a government agency, over the precedent and emotion induced by a particular decision. Perhaps most of all, they divert our attention from a world of immense complexity, nuance, and ambiguity.

To combine theory with narrative and other forms of empirical inquiry is to court bewilderment. Historians, journalists, and close observers of American pharmaceutical regulation may well wonder what a theory brings that they did not already know. Academics and other readers whose interest is in

³⁰For examples of the simpler narratives, see Peter Temin, *Taking Your Medicine: Drug Regulation in the United States* (Cambridge: Harvard University Press, 1980); Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What To Do About It* (New York: Random House, 2004); Richard Epstein, *Overdose: How Excessive Government Regulation Stifles Pharmaceutical Product Innovation* (New Haven: Yale University Press, 2007). For previous criticisms and corrections to Temin's scholarship, see Harry M. Marks, "Revisiting the Origins of Compulsory Drug Prescriptions," *American Journal of Public Health* 85 (1) (1995): 109–15; and *The Progress of Experiment* (New York: Cambridge University Press, 1997). Angell offers a revealing examination of FDA policy in recent years (see esp. 208–16), but her narrative often oversimplifies matters, particularly in discussing the FDA's drug approval standards and behavior (see pages 75–6, 93, 243 of Angell, and my notes on some of these simplifications in the chapters that follow). Minimal and misleading portraits of American pharmaceutical regulation inform some of the leading theoretical writings on regulation; Stephen Breyer, *Regulation and Its Reform* (Cambridge: Harvard University Press, 1982), 132 (characterizing FDA officials' emphasis on safety issues as induced by economic and political pressures rather than the strict and historical construction of congressional statute that many FDA officials actually followed when he wrote); in 1994, Breyer was appointed an Associate Justice of the Supreme Court. See also W. Kip Viscusi, Joseph E. Harrington, and John M. Vernon, *Economics of Regulation and Antitrust*, 4th ed. (Cambridge: MIT Press, 2005), chap. 24. Philip Hilts provides one of the more comprehensive treatments in recent years—particularly his narratives from the 1980s onward); *Protecting America's Health: The FDA, Business and One Hundred Years of Regulation* (New York: Knopf, 2003)—yet his narrative too offers a number of misleading generalizations, some of which I detail in the chapters that follow. Former FDA general counsel Richard Merrill has thoughtfully surveyed some of the criticisms and simplifications of recent decades in "The Architecture of the Government Regulation of Medical Products," *Virginia Law Review* 82 (1996): 1754–5, n.2–4.

the construction of models and simplified representations of political reality will ask why one needs detailed narratives to express what can be more simply and universally conveyed by “theory.”

My hope is to explore the interface between theory and evidence in ways that are “positivist” or somewhat causally descriptive as well as interpretive. The intertwined concepts of reputation and power are intended to illuminate not only the dynamics and history of American pharmaceutical regulation, but also patterns in other forms of government regulation. In the sense of “normal science,” a theoretical approach based upon organizational reputation can offer predictions and expectations that historical and empirical study can falsify or support. If this approach helps to account for the puzzles of American and global pharmaceutical regulation, then it may help in understanding other policies and their development. If it does not, then other approaches and explanations might be sought out. From this perspective, I will focus repeatedly on the sorts of expectations that emerge from a reputation-based account of pharmaceutical regulation that would not emerge readily from other perspectives.³¹ The “value added” of a reputation-based account in this strict positivist sense is that it generates predictions and accounts for empirical and historical patterns that other theories cannot. It would be impossible to understand the FDA’s regulatory power over the development and marketing of heart medications—and the case of tissue plasminogen activator in particular—without a narrative approach that emphasized the contingency, the ambiguity, and the unanticipated outcomes of human decision.

Yet the value of theory in studying complex phenomena is not limited to prediction and testing alone. Theory also guides interpretation. It can supply a new lens or alternative vantage point from which to re-encounter the previously familiar. It can highlight previously unexamined facets of the problem. With a theoretical lens and appropriate circumspection about what it can accomplish, an observer can make sense of otherwise puzzling patterns of behavior and action, otherwise opaque institutions and structures. Or the scholar can point to what seems sensible, expected, and tidy and suggest otherwise. Theoretical metaphors are not necessary for scholars to engage in these practices, but they can help.

Another reason for weaving back and forth between narrative and theory comes from the limitations of social science. Modern social science and statistical analysis tend to examine political and economic reality as if they were data generated in an experiment, as a sample of various cases that can be compared apple-to-apple. Like other scholars, I rely heavily upon such comparisons in this book. In some cases the comparisons are explicitly quantitative—the worlds studied are assumed to be those in which measurements are taken (a drug is approved in nine months, seven black-box warnings are added to drugs within a year, thirty votes are cast in favor of an amendment to drug legislation). In these cases, in which events and meaning

³¹These historical and empirical expectations are elaborated in the following chapter, and some of them appear more specifically in the thematic chapters (chapters 7–11).

are countable and sometimes even “commodified” such that the outcomes can be indexed by measurements (utilities, currency, other indices of value) that can be bought and sold in markets that are both implicit and explicit.³²

The problem is that political life—and, for that matter, much of scientific life, social life and, economic life—does not often produce experimental data. And very often the assumption of countable reality does more harm than good. Quite commonly political life fashions and constrains patterns of activity and contest that cannot be understood without careful narrative and attention to contingency. The patterns of interest in pharmaceutical regulation are highly sequenced configurations of behavior in which an entire history of context and past action, combined with actors’ visions, emotions, and expectations of the future, are necessary for understanding the process and the outcome. In part for this reason, close observers of (and participants in) the subject of study often see that simple scientific theories of their world do not pass what one colleague of mine calls “the dense knowledge test”: Does a theoretical model generally, and an empirical account specifically, make sense to those most thoroughly and intimately aware of the action? Do quantitative analyses count up events that historians, ethnographers, and careful observers of the events would never consider comparable in the “apple-to-apple” sense? When scholars of international security claim to discover a correlation between economic growth and the incidence of “civil war,” do they do so anachronistically by aggregating events (deaths, battles, patterns of ethnic strife, acts of physical, sexual, and emotional violence) that may be difficult, and perhaps impossible to compare to one another? Do these aggregations make sense of human emotions, meanings, memories, and political consequences attached to these events?

An animating principle of this study, then, is that narrative, quantitative, and comparative approaches can, indeed must, complement one another in the study of global pharmaceutical regulation and its historical development. My hope is not to attain a perfectly happy medium among the methods; indeed, the tension among the methods is itself productive. The combination is powerful when the different methods point to similar patterns, as well as when the use of one kind of method points to difficulties in what one can learn from the others.

THE SUBJECT, THE THEORY, AND THE APPROACH

Reputation and regulatory power both live at an interface—the interface of subject and audience, the interface of regulator and regulated. In studying the intertwined reputation and power of the U.S. Food and Drug Administration, I have found it necessary to examine not just statutes, rules, public

³²The assumption of “countable additivity” to which I refer here is helpfully clarified in Patrick Billingsley, *Probability and Measure*, 3rd ed. (New York: Wiley, 1995). A more technical treatment that expands upon these notions and relates them to weak convergence concepts is Billingsley’s *Convergence of Probability Measures*, 2nd ed. (New York: Wiley, 1999).

decisions, and directives, but also concepts, perceptions of action, the reception of an organization and its behavior in various audiences embedded in courts, in public opinion, in congressional committees, in journalism and its readers and viewers, in circles of professional and scientific judgment. And in the analysis of reputation and power in regulation, it is not only the regulatory official but also her audiences and subjects that merit attention (perhaps most of it).

At its core, the study concerns the administrative governance of a particular kind of commodity—the “pharmaceutical,” the “ethical drug.” Definitions of “drug” have changed immensely over the twentieth century, and there has always meaningful overlap between the worlds of “foods” and “drugs.” An immense quantity of products officially regulated as “foods” today are profitable because they make therapeutic claims—herbal remedies, nutritional supplements (variously known as “nutri-ceuticals”), organically cultivated foods and others. The tale of how these have eluded FDA regulation is itself interesting and is taken up briefly in chapters 5 and 6. Quite differently, a range of prescription products attempts to provide nourishment—parenteral nutrition therapies form one example.

Much of the study is focused not on newer forms of medical therapies but upon a set of drugs that the FDA has called “new molecular entities.” In the pharmaceutical world, two categorical distinctions are often employed to break apart the continuous and slippery space of drugs. Molecular entities are usually distinguished from “biologics.” The world of biologics is often wrongly conflated with the world of “biotech,” when in fact most biotechnology drugs are not vaccines or otherwise bioactive. A more pervasive difference is between “small” and “large” molecules, such that the larger molecules represent proteins and antibodies that are “biologically active,” whereas the smaller molecules stand in for more traditional drugs without biological activity.³³

Pharmaceutical regulation touches upon politics, law, medicine, science, business, and foreign affairs. In writing this book, I have incorporated methods and insights from many disciplines—history, pharmacology, political science, law, medicine, public health, mathematical finance and economics, sociology, mathematical statistics, and anthropology. To be frank, I have mastered none of these trades, and this book represents a highly imperfect combination of research methods. It is my hope that blending these different disciplines and methods—the combination of historical narrative with statistical analysis, the examination of power in agenda setting as well as in concept formation, the adoption of anthropological notions of group image

³³“Large molecules” and “macromolecules” often refer to nucleic acids, enzyme mimetics, and monoclonal antibodies; the history of American pharmaceutical regulation with these products has not been well narrated, and the FDA’s experience with such products forms a small portion of the study. Even the binary distinction of “small” versus “large” molecules misleads. The difference is often a matter of degree and of interpretation about the drug’s access to target cells (a mistake I have made myself more than once). For a helpful summary review, consult Michael P. Murphy and Robin A. J. Smith, “Drug Delivery to Mitochondria: The Key to Mitochondrial Medicine,” *Advanced Drug Delivery Reviews* 41 (2000): 235–50.

on the one hand, and on the other, approaches to reputations as depreciable assets in which certain forms of investment take place—will illuminate more than it obscures.

The study reported here is the result of intensive research carried out over many years in the archives of government agencies, major research and specialty hospitals, chemical and pharmaceutical corporations, the U.S. Congress and its members and committees, selected presidents of the United States and their appointees, disease and patient advocacy organizations, medical associations and scientific groups, university medical centers, and other relevant organizations and institutions. Although the subject of analysis is an organization of the U.S. government, the audiences for that organization span the globe. The study therefore relies upon primary and secondary materials from other nations and non-English languages. With a few exceptions, most of the primary sources used have never before been consulted or cited in published research. I say this primarily to convey a sense of caution. Further engagement with the materials used in this study will undoubtedly produce richer and more accurate portraits than I have elaborated here.

The world of pharmaceutical regulation is subtended by a vast number of trade reporters, newspaper reports, business and finance journals, science magazines, medical journals, and, at this writing, “web logs” available on the Internet. I have purposefully scoured a large number of these sources, in part to get a better sense of the FDA’s varied images, and in part to observe the same events from different standpoints. The study often relies upon these published or written documents for narrative and statistical data. This is not the same as studying “what people say” as opposed to “what they do.” For one, many of the writings and remarks are observations on others’ behavior. In many other cases, the documents reveal behavior in aggregate statistics or in relatively consensual narratives of the interaction between government officers and the social and economic concerns they regulate.

I have also conducted many interviews over the past fifteen years in studying American and global pharmaceutical regulation. These have been important, though I have not taken them as the primary evidence for the study. My reliance upon documents forms a basic limitation of the book, insofar as important lessons about the FDA and other regulatory agencies have been generated from in-depth interviews conducted and interpreted by observers with long and familiar knowledge of the agency and the policies it administers.³⁴ A central reason for this reliance upon documents comes from what I was able to obtain from interviews and conversations. In many cases, depictions of events that I took from interviews as factual were, upon further study and reflection, simply one reading (among many) of crucial and pivotal events. As I came to do more of them, I found that interviews were important less for establishing “what actually happened” and more for getting a sense of different lenses through which the same facts, the same choices, the same rules, the same organization might be viewed. For this reason, I

³⁴Hilts, *Protecting America’s Health*; Hawthorne, *Inside the FDA*.

interviewed not only “participants” but also observers—reporters who regularly covered the FDA, physicians who testified before or who sat upon federal advisory committees, company scientists who did not deal directly with the agency but whose impressions (taken at one or more removes from those who did) were nonetheless of great value.

In the first part of the book, I offer a set of overlapping narratives in the hope of describing and explaining the evolution of the FDA’s organizational reputation and its power. These powers are ever changing, but a relatively stable structure of robust directive, gatekeeping, and conceptual power had crystallized by the late 1960s. In chapters 2 through 4 I elaborate the development of reputation and power at the FDA through the thalidomide crisis of the early 1960s. These narratives embed comparisons to other realms of regulation and other nations. They show how the Administration’s regulatory power developed—from legislative enactments that embodied the FDA’s strong public reputation, from the acquiescence of professional and scientific bodies that ceded their powers to the FDA or allied with the Administration in their exercise, and from rulemaking and administrative behavior. In chapters 5 and 6 I discuss patterns by which the FDA’s reputation in the modern pharmaceutical world were cemented and contested, not least the legitimation of broad regulatory power by American courts and the challenges to regulatory power posed by business and professional interests and by the rise of new paradigms of illness (modern cancer and AIDS and other disease-based constituencies).

The second part of the book reveals the structure of reputation and power thematically, less in the form of a progressive narrative and more in the form of a subject-based discussion of different features and realms of pharmaceutical regulation. The worlds I describe—the political economy of new drug approval (chapter 7), the regulation of clinical research and drug development (chapter 8), the advisory committee system (chapter 7), post-market surveillance (chapter 9), the dance of firms and regulators (chapter 10), and the international system of pharmaceutical regulation (chapter 11)—are not static entities. Yet in their contours, and in the way they are shaped by gatekeeping power and organizational reputation, they bear some meaningful stability. In each of these realms, moreover, a reputation-based perspective on regulatory power offers predictions and interpretations that garner the weight of evidence on numerous dimensions. I elaborate upon recent changes in chapter 12.

A more functional reading of the book is that the first part is about origins, the second about operation. The first part of the book describes how reputation and power created the modern system of pharmaceutical regulation. The second part describes the everyday operation of that system in terms of reputation and power, and it describes the mutual influence of audience and regulator in the realm of regulatory process, firms and research organizations, and the global arena.