

## **“Corrosive Capture? The Dueling Forces of Autonomy and Industry Influence in FDA Pharmaceutical Regulation”**

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Modern government offers few if any agencies more powerful, more watched or more pressured, than the U.S. Food and Drug Administration (FDA). Rough estimates suggest that the FDA regulates over one quarter of U.S. gross domestic product, with primary responsibilities for food, pharmaceuticals and medical devices, cosmetics and, since 2009, tobacco products. Over a wide range of these products – drugs, medical devices, food additives, and certain tobacco products -- the FDA has expansive gatekeeping power: the congressionally mandated task of deciding whether the products in question can be marketed at all. Gatekeeping power has many facets. Gatekeeping can be used to protect the public or provide it with false confidence; create market-wide confidence in new products; enhance or stifle innovation (often both); snow and guile consumers into thinking that poor, unsafe products are safer and better than they are; and hone the production, dosage and information about drugs to help doctors and patients optimize their use.

If ever there were a plausible prima facie case for capture, a gatekeeping regulator like the FDA would seem to provide it. In its governance of pharmaceuticals, the FDA regulates a vast industry, one that supplies a global market approaching one trillion dollars in size. Given its size and its historical connections to science and technology, this industry possesses broad economic, political and cultural power. When Sam Huntington and Marver Bernstein wrote about the potential capture of regulatory agencies in the 1950s and 1960s, it was with just such an agency-industry

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relationship in mind (though neither wrote on the FDA). Large industries like these would seem to be primed to limit entry and preserve market access for themselves. And when George Stigler looked for examples when “regulation is acquired by the industry,” he found his examples among entry-limiting regulation: weight limits for trucks (shaped by the lobbying of railroads and farmers) and occupational licensing (where those with market power limit the entry of their potential competitors, restraining supply and inflating equilibrium price).

In this chapter I elaborate on the possibility of regulatory capture at the FDA and its potential mechanisms. Using traditional definitions of, and evidence for, capture as Huntington, Bernstein and Stigler and their successors wrote about it, I conclude that until the late 1990s, there is little strong evidence of systematic or widespread capture of the FDA by the American or global pharmaceutical industry. There is, to put it simply, abundant evidence against the idea that American pharmaceutical regulation has been built through the attempts of drug companies to limit entry and preserve market power. Examining the prospect of capture through other mechanisms, however, suggests a possibly different conclusion. A degree of “cultural capture” of the FDA may have occurred, but the hypothesis needs further refinement and investigation. If this capture occurred, it is not of the entry-barrier form, but is rather of the *corrosive form* whereby deregulation is accomplished, not through republican mechanisms but through cultural capture of regulatory institutions. And under no circumstances does the evidence support the “strong capture” welfare hypothesis that the FDA is so captured that the public would be better off without this form of regulation.

Before turning to a review of the historical and statistical evidence on FDA capture, I

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examine the idea of corrosive capture and how it might be applied to deregulatory efforts in pharmaceutical regulation and other realms of regulation.

### **The Idea of Corrosive Capture**

Special interests and regulated industries can shape policies in different ways, and they can push policies in several directions. The Stiglerian account of capture predicts that *captured regulation will be stronger* in the sense of more rigid and less permeable entry barriers to the market. If the industry is using regulation to form a cartel and restrict supply and/or entry, then captured regulation will be more effective for these aims to the extent that it is *more effective* in terms of achieving its stated aims, that is, to the extent that the entry barriers are strong. If physicians seek to limit the supply of their services and thereby raise their pay, then licensing needs to present higher hurdles to qualification and entry for prospective doctors.

Corrosive capture, on the other hand, occurs if clearly organized firms push the regulatory process in a “weaker” direction, not with the aim of reducing entry, but with the aim of reducing costly rules and enforcement actions that reduce firm profits. This is a form of deregulation, of course, but it is quite plausible that deregulation through electorally sanctioned mechanisms would not present as much of a policy problem as deregulation by cultural capture. The corrosion of regulation occurs not with the express sanction of voters in repeated elections, but in the weakening of regulatory independence – and the fidelity of regulators to their statutory obligations – through various forms of capture.

It is important to recognize that much if not most of the public and academic discussion

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about capture in recent decades is about regulatory corrosion. Hence the capture and regulatory failure of the past few decades is distinct from the kind that Huntington, Bernstein and Stigler were concerned with in the middle twentieth century. Entry-barrier capture was the process by which regulators intervened in markets with the effect of privileging one set of producers over another (the railroads and trucking regulation, the Civil Aeronautics Board) and often producers over consumers altogether. But in these early models, it was the application of regulation directly to markets and firms that marked capture, not the application of deregulation or weak regulation.

By contrast, it is apparent that as far as plausible capture is concerned, something quite different was going on over the past several decades. It was capture evinced in the weak application (or non-application) of regulatory tools. In other cases it was the application of jurisdictional boundaries to prevent other agencies from regulating. Regulatory pre-emption – the move by which state and local regulations are invalidated by the imposition of national-level supremacy – became a favorite tool of officials in the George W. Bush Administration as means of achieving deregulation. In some cases pre-emption of state regulation was asserted by regulatory agencies themselves, such as when the Office of Thrift Supervision (OTS) and the Office of the Comptroller of the Currency (OCC) issued rulings in the 1990s and early 2000s pre-empting the application of state mortgage laws to federal thrifts and national banks.<sup>1</sup> Another form of boundary manipulation comes in regulatory arbitrage, or when banks choose their markets or institutional form so as to fit themselves to the least rigorous regulator.

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<sup>1</sup> Kathleen Engel and Patricia McCoy, *The Subprime Virus: Reckless Lending, Regulatory*

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The plausible mechanisms of corrosive capture are, to some degree, well known from the literature on capture in general. Firms and industries that want lower regulation, relative to the preferences of the public and or the regulatory aims expressed in statute, will rely upon campaign contributions, pressure upon politicians and perhaps the “revolving door” to reduce their individual and collective regulatory burdens. Yet another mechanism is available, one hard to prove, but one that seems to me increasingly relevant: what James Kwak, in this volume, terms “cultural capture.” It is always possible that cultural capture, through the shaping of assumptions, lenses and vocabularies, can be used to support more traditional forms of Stiglerian capture. Yet cultural capture seems less likely to be deployed for the erection and maintenance of entry barriers than for deregulatory purposes. It would seem easier for industry to coordinate on a single message to reduce regulation – the benefits are industry-wide and the losers in this process are probably consumers – than to coordinate on a message in which some firms win and other firms (even if they are weaker or smaller) lose. So too, the innovation and laissez-faire ideologies that have shaped regulation in the past thirty to forty years have been deregulatory in their aim, and the existing accounts of cultural capture emphasize these ideological framings as central to recent developments in financial regulation.

### **Pharmaceutical Regulation: A Review of Institutional Development**

*The Food, Drug and Cosmetic Act of 1938.* The idea of regulatory entry barriers as a function of capture is one that invokes (implicitly or explicitly) a model of regulatory legislation. When regulation limits entry, then the benefitting firms are likely to have bought this protection

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though inducements to legislators.<sup>2</sup> If such a stratagem had worked to secure entry barriers for the larger and better establish pharmaceutical firms of the early twentieth century, then the focus of analysis should be upon the Food Drug and Cosmetic Act of 1938.<sup>3</sup>

The agenda-setting process for the 1938 Act came from various calls for a revision of the FDA's original enabling statute, the 1906 Pure Food and Drugs Act. As historians have documented, two forces – the FDA itself and organized women's groups – exercised strong leverage in pressing for changes to the 1906 law.<sup>4</sup> FDA officials had long been disappointed with the operation of the 1906 Act. The first bill addressing these problems was authored by FDA personnel, was sponsored by New York Senator Royal Copeland, and was titled "S. 2800." Along with its successors "S. 5" and "S. 1944," S. 2800 attempted to rein in the patent medicine industry. One might temptingly interpret this bill, and its successors, as plausible candidates for placing

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<sup>2</sup> Gene Grossman and Elhanan Helpman, *Special Interest Politics* (Cambridge, MA: MIT Press, 2003).

<sup>3</sup> This section draws on both older and newer literatures on the 1938 Act. Charles O. Jackson, *Food and Drug Legislation in the New Deal* (Princeton: Princeton University Press, 1970). James Harvey Young, *The Medical Messiahs: A Social History of Health Quackery in Twentieth-Century America* (Princeton: Princeton University Press, 1967). Daniel Carpenter and Gisela Sin, "Policy Tragedy and the Emergence of Regulation: The Food, Drug and Cosmetic Act of 1938," *Studies in American Political Development*, 21 (2007): 149-180; Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton: Princeton University Press, 2010), Chapter 2.

<sup>4</sup> Oscar E. Anderson, *The Health of a Nation: Harvey W. Wiley and the Fight for Pure Food*, (Chicago, University of Chicago Press, 1958); James Harvey Young, *Pure Food* (Princeton: Princeton University Press, 1990); Daniel P. Carpenter, *The Forging of Bureaucratic Autonomy: Reputations, Networks and Policy Innovation in Executive Agencies, 1862-1928* (Princeton: Princeton University Press, 2001), Chapter 8.

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competitive and entry barriers upon the primary competitors of established pharmaceutical operations. The patent medicine industry was, after all, a multi-million dollar market in the early twentieth century. The S. 2800 bill required disclosure of ingredients on labels (something that established drug companies like Abbott, Pfizer and Parke-Davis did, but which patent medicine companies did not), and removed the 1906 Act's condition that the FDA had to prove intent to defraud in order to seize commodity shipments. It also gave the FDA power to seize multiple shipments of "misbranded" goods, and rendered advertisers and manufacturers alike legally liable for fraudulent claims. S. 2800 also empowered the FDA with new tools to govern pharmaceutical advertising. S. 5 weakened a number of these provisions, but remained a strong entry-constraining bill for the patent medicine industry and for many fledgling outfits in pharmaceuticals.

To advance these bills on the congressional and national agendas, the FDA launched a publicity initiative aimed at demonstrating the hazards of adulterated food and medicines to the nation's press. The FDA had been prevented from direct lobbying and publicity efforts in the Deficiency Appropriations Act of 1919, yet the agency circumvented this constraint, distributing pamphlets such as the one entitled *Why We Need a New Pure Food Law* and allowing its officials to make radio addresses on S. 2800. FDA Information Officer Ruth Lamb successfully invited press outlets to cover Copeland's first Senate bill (S. 1944), and she used her own time and money to author a popular book on the hazards of patent medicines entitled *The American Chamber of Horrors* (1936).<sup>5</sup>

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<sup>5</sup> Gwen Kay, "Healthy Public Relations: The FDA's 1930s Legislative Campaign," *Bulletin of the History of Medicine* 75 (2001) 446-487.

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FDA officials also drew strength from their decades-old alliances with women's groups and organized consumer unions. Two women's groups – the General Federation of Women's Clubs (GFWC) and the Women's Christian Temperance Union (WCTU) – some of the most powerful lobbies of their time, almost single-handedly waging successful campaigns for mothers' pensions and child-labor laws. With FDA facilitation, these two groups had been instrumental in lobbying for the 1906 Act. In the 1930s debates they were joined by Consumers' Research (CR). CR was founded in 1929 with 1,000 members and by 1933 had ballooned to 45,000 members. As historian Charles Jackson describes the union, "CR's influence and significance far exceeded its actual membership. The organization served as a coordinating body for Congressional and other sympathizers of consumer legislation." Rexford Tugwell found "astounding" the "receptive attitude of the general public" towards CR.<sup>6</sup>

Despite what might seem like favorable circumstances in the early New Deal – an overwhelming Democratic majority in Congress with pro-regulation impulses, a Democratic president, supportive women's groups and a well-coordinated rhetorical campaign – several factors combined to blunt the FDA's initiative for food and drug law reform. The most salient was well-organized and well-represented opposition from the affected industries. As Jackson describes the rise of opposition, "Many existing trade bodies were turned almost immediately into vehicles of

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<sup>6</sup> Carpenter, *The Forging of Bureaucratic Autonomy*, Chapter 8; Skocpol, *Protecting Soldiers and Mothers* (Cambridge: Harvard University Press, 1992); Clemens, *The People's Lobby* (Chicago: University of Chicago Press, 1998). Jackson, *Food and Drug Legislation in the New Deal*, 20-21.

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resistance. Especially militant were the Proprietary Association [PA] and the United Medicine Manufacturers of America [UMMA].” The PA and UMMA sponsored protest gatherings, radio advertisements, and coordinated petition campaigns against FDA-strengthening bills. The manufacturers found able legislative defenders such as Senators Josiah Bailey of Tennessee and Arthur Vandenberg of Michigan. Two of the legislation’s sponsors – Senator Copeland himself and Rexford Tugwell – also had the disadvantage of having well-ensconced political enemies, with FDR himself displeased with Copeland and many New Deal opponents hammering Tugwell as a symbol of what they perceived as the Roosevelt Administration’s new liberal arrogance.<sup>7</sup>

Reform opponents landed an apparent deathblow in 1935, when the Senate passed Copeland’s S.5, but only after attaching the infamous “Bailey Amendment” which vitiated the measure. The Bailey amendment prohibited the FDA from regulating any aspect of pharmaceutical advertising and would give all such control to the Federal Trade Commission (FTC). From the vantage of the 1906 law, where the FDA had control over fraudulent advertising, this was a step backwards for the FDA. Once the Bailey Amendment was approved, S. 5 passed the Senate but was doomed by criticisms from the left and the right. S. 5 then died in the House by a substantial 190-70 vote.

Roll call votes are available for three crucial votes on the Senate measure in the 74<sup>th</sup> Congress (1935-1936), and these votes can be examined to test for the impact of observed ideology, party, region and organized interests. The first two votes were on procedural measures to reconsider

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<sup>7</sup> Jackson, *Food and Drug Legislation in the New Deal*, 38-39.

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an amendment that had been attached to S.5 during committee. Those who favored a stronger FDA wanted to revisit the committee's decisions and voted "yes" on this measure. The third vote was a vote on the Bailey amendment prohibiting the FDA from regulating pharmaceutical advertising. Proponents of reform voted "no" on this measure, while most opponents of reform voted to pass it. Probit regression analyses of these three votes in the 74<sup>th</sup> Congress were conducted, and coefficient estimates appear in Table 1. The control variables are chosen to unearth patterns of support for FDA-strengthening regulation before the sulfanilamide disaster. The most important of these controls are two general measures of ideology or voting propensity, namely first and second-dimension D-NOMINATE scores. Also included are the senator's party (1 if Democrat) and the underlying Democratic strength of his constituency, measured by the percentage of vote for FDR in the 1932 election, and a variable measuring the shift in voter support for FDR from 1932 to 1936 as a way of measuring political trends within each state. To these political covariates are added demographic and economic variables measuring the state's rate of unemployment in 1930, the percentage of its residents aged 18-20 in school, the percentage of its residents who were illiterate as defined by the Census, the percentage of its residents who were African-American.<sup>8</sup>

Two variables measuring the presence of organized patent-medicine and pharmaceutical manufacturers in a state are included to test industry capture and rent-seeking hypotheses. The first measures the number of industry members of the Proprietary Association whose headquarters were

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<sup>8</sup> On NOMINATE-based methods and their application to American political history, see Keith Poole and Howard Rosenthal, *Congress: A Political-Economic History of Roll-Call Voting* (Oxford University Press, 1998).

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in a state. The second measures the number of primary (above associate) members of the United Medicine Manufacturers' Association whose headquarters were in a state.

A key result from the Table 1 regressions is that rent-seeking hypotheses are strongly rejected. The variable measuring UMMA firms headquartered in a state is negatively associated with “yes” votes for the first two reconsideration measures and positively associated with votes for the Bailey amendment. In other words, *pharmaceutical interests aligned themselves against the entry-constraining legislation, and their legislative representatives followed suit.*<sup>9</sup> In addition, senators from states with higher unemployment rates were more likely to support the reconsideration measure, which may reflect anticipated effects of tighter regulation upon proprietary manufacturers in the state. This result is not, however, predicted by a rent-seeking perspective.<sup>10</sup>

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<sup>9</sup> The variable measuring state-level presence of proprietary manufacturers is insignificant at the  $p < 0.05$  level in all regressions. The coefficient estimate for the PA measure does achieve significance at the  $p < 0.10$  level in the model for the first reconsideration vote, but this is due to the fact that this measure is highly correlated ( $\rho = 0.5598$ ) with the UMMA measure. Once the UMMA measure is removed, the coefficient estimate for the PA measure in this model switches sign and becomes insignificant ( $b = -0.00029$ ;  $z = -0.019$ ). This is not true for the UMMA measure, which remains negative and statistically significant in the first two models and positive and statistically significant in the third model when the PA measure is removed.

<sup>10</sup> The control variables are not particularly notable for their estimates, as they support standard legislative politics accounts of voting on these issues. The first dimension D-NOMINATE score (measuring left-right “economic ideology,” roughly) has a negative coefficient estimate in the first two regressions and a positive estimate in the third. Since higher scores indicate more conservative members, this result implies that more liberal senators were more likely to vote for the first two measures and less likely to vote for the third. Conditioning on this effect, Democrats appear to be slightly more likely to vote against FDA-strengthening legislation, but these coefficient estimates are statistically indistinguishable from zero. The variables measuring support for FDR are also insignificant, suggesting that underlying Democratic support in one’s constituency did not, net of other factors, induce more or less support for reform.

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Rent-seeking and industry capture explanations are not, then, supported by these analyses of legislative votes on entry-constraining regulation. Indeed, a hypothesis which runs *counter* to the capture perspective receives strong support. *Affected industries, particularly the organized pharmaceutical firms that would have benefited from reduced proprietary competition, nonetheless fought the legislation, and their representatives were more likely to vote against FDA-strengthening measures.*

In the end, the Food, Drug and Cosmetic Act of 1938 would pass, with even stronger gatekeeping provisions than envisioned in the earlier bills. In the wake of the sulfanilamide tragedy of 1937 and 1938, when an otherwise common sulfanilamide ingredient was suspended in a highly toxic elixir and over 100 Americans died, Congress acted quickly to give FDA officials the gatekeeping power that they had long sought, and that they viewed as particularly necessary in light of the tragedy.<sup>11</sup> The legislation defined the concept of a new drug and stipulated that any new drug must be approved by the FDA on the basis of its demonstrated safety.

*Post-1938 Developments.* The tale of the FDA's enabling legislation in pharmaceutical regulation – the law that gave the agency gatekeeping power over the new drug marketplace – offers a stark rejection of capture-based hypotheses. This was a law passed largely through consumer pressure, pressure that had become incredibly amplified in the wake of a tragedy, and its

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<sup>11</sup> Carpenter and Sin, "Policy Tragedy and the Emergence of Regulation: The Food, Drug and Cosmetic Act of 1938."

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gatekeeping provisions were resisted by the very companies that would benefit from them.<sup>12</sup> A similar inference can be drawn from developments in the 1940s and 1950s, when the FDA began to flesh out its regulatory power by establishing precedents through operations, decisions and enforcement. The predominant influence upon the agency during this period came from a set of multiple constituencies and audiences at the nexus of academic pharmacology, government and university scientists, and industry. There was industry participation in the process, to be sure, and drug companies and their political representatives had occasional successes in resisting regulatory expansion. Yet the development of the new drug application and the emergence of drug efficacy standards (whereby the FDA would assess drugs not only for their toxicity but also for their therapeutic results) happened far more outside of industry circles and influence than within them. By the time that another policy tragedy – the thalidomide crisis of the early 1960s, in which a commonly used sedative induced thousands upon thousands of birth defects – came along, the FDA was already regulating efficacy in new drug applications and imposing a scientific and procedural stringency that had alarmed the industry. Much of this stringency was codified and further elaborated in the Drug Amendments of 1962 that followed the thalidomide crisis. It was from the rulemaking following this statute (the Investigational New Drug (IND) rules of 1963) that the three-phase system of testing that governs global pharmaceutical development was hatched and codified.

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<sup>12</sup> It should be clear that drug companies in the New Deal and in the early 1960s likely perceived that there would be other costs – such as increased regulatory scrutiny of their research and development processes, their products and their marketing operations – that would outweigh whatever supply restriction benefits they derived from these new laws and regulations; Carpenter, *Reputation and Power*, Chapters 2 through 4.

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In these critical developments, the organized pharmaceutical industry largely played the role of an observer.<sup>13</sup>

There were more successful industry attempts in the years following the 1962 Amendments to shape the dialogue on regulation. Through a series of articles and books partially sponsored by industry, and supported and often hosted and published by the conservative American Enterprise Institute (AEI) in Washington, D.C., clinical pharmacologists and industrial organization economists began to question the effect of FDA governance upon a new watchword: “pharmaceutical innovation”. These arguments were led by clinical pharmacologists Louis Lasagna and William Wardell, and economists Sam Peltzman, Henry Grabowski and John Vernon, among others. In addition to the focus of attention upon the broad concept of innovation, these scholars coined a term – the “drug lag” – that refocused the international comparison on how quickly drugs reached the market in the United States versus comparator nations, especially Great Britain. The conclusions of these analyses were generally that the FDA’s regulatory stringency had the effect of depriving American doctors and their patients of the latest advances in the pharmaceutical armamentarium. The critiques were highly effective, so much so that the FDA internally began tabbing some of its drug applications as “drug lag drugs” once another country had approved them,

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<sup>13</sup> Carpenter, *Reputation and Power*, Chapters 3 and 4; see also Philip Hiltz, *Protecting America’s Health: The FDA, Business and One Hundred Years of Regulation* (New York; Knopf, 2003). The National Cancer Institute (NCI) also played an important role in the development of phased clinical trials, yet the available evidence suggests that the idea of sequenced studies for examining toxicity and effectiveness was one that emerged from the U.S. Department of Agriculture and the FDA, and it pre-dated the concrete notions of phased studies in the NCI.

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and also began approving many drugs at the end of the year (a so-called “December effect”).<sup>14</sup>

To the extent that a deregulatory trend has shaped the FDA, it came as much from unlikely capture sources – organized patient advocates and government health officials – as from drug companies and their political organizations. Beginning with critiques about the drug lag and crystallizing in battles over cancer therapeutics and AIDS medicines, the FDA began to demonstrate greater flexibility in its drug development rules and its approval decisions. The transformation occurred first in the FDA’s governance of cancer drugs, not least because forceful voices in oncology circles had begun to complain loudly about FDA interference in their clinical experiments, and because the National Cancer Institute (the largest and most powerful arm of the National Institutes of Health) had begun to legitimate these complaints. In the late 1970s and early- to mid-1980s, before the AIDS crisis began to occupy health officials and drug development experts, the FDA moderated its stance and imported flexibility to its clinical development guidelines for cancer.<sup>15</sup>

When the AIDS crisis hit, other government health agencies such as the NIH and the Public Health Service (PHS) initially launched into action to identify the pathogenesis of the disorder and to isolate potential molecular treatments. It was not until after the first AIDS drug approval (azidothymidine, or AZT) that AIDS patients and gay men’s groups began to coalesce around an agenda of FDA reform. AIDS activists did this cautiously, wary of alliances with the

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<sup>14</sup> Carpenter, *Reputation and Power*, Chapters 5, 7 and 12; Hilts, *Protecting America’s Health*, “The Drug Lag.”

<sup>15</sup> Carpenter, *Reputation and Power*, Chapter 6.

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pharmaceutical industry. Yet this moment, and the overwhelming public and professional anxiety induced by the globalizing AIDS epidemic, saw industry-backed lobbyists and conservative voices seize an opportunity to create a strange-bedfellows coalition in support of FDA transformation. The longer-term result was the Prescription Drug User Fee Act (PDUFA) of 1992, which levied per-application taxes upon drug companies in return for greater industry voices in FDA management and FDA observance of deadlines in new drug review. PDUFA is widely acknowledged to have accelerated the agency's review of new drug applications.

Many agency observers and critics have argued that the user-fee law represents a form of agency capture, insofar as the FDA depends for its funding upon the industry it regulates. This interpretation is plausible but lacks solid evidence and, in the most simplistic of cases,<sup>16</sup> rests upon a misunderstanding of PDUFA's history. The user-fee act was a compromise between liberal Democrats (headed by the late Senator Edward Kennedy of Massachusetts) and conservative Republicans (represented by Senator Orrin Hatch of Utah). Kennedy and Hatch co-sponsored the bill, and it passed the U.S. Senate unanimously; few if any of its sponsors at the time saw it as a deregulatory measure. If corrosive capture was the result of PDUFA, it cannot be said to have been an intended result.

The problem with representing PDUFA as a cause of agency capture – clearly the critics have in mind the corrosive form – is that its emergence coincides with a number of other plausible explanations. These include the following:

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<sup>16</sup> Marcia Angell, "FDA: This Agency Can Be Dangerous," *New York Review of Books*, September 2010.

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- The more conservative and anti-regulatory climate of the 1980s and 1990s, one that was reinforced in presidential elections and congressional policymaking;
- The AIDS crisis itself and its related calls for acceleration of the FDA approval process;
- The information technology revolution occurring in society, whereby new drug applications and a host of other government functions have been completed more quickly;
- The increasing staff totals at the FDA, which permitted quicker new drug reviews, and which began at least five years before the user-fee act was struck into law.<sup>17</sup>

Any claim that the user-fee act is the proximate cause of corrosive capture, or even that capture has occurred in the past fifteen to twenty years of American pharmaceutical regulation, must contend with these alternative explanations. Simply put, those claiming that capture has occurred have failed to provide anything but anecdotal evidence and policy testimonials.

Perhaps the most plausible mechanism for capture to have occurred is that of cultural capture. The revolving door hypothesis is unlikely to explain recent changes, insofar as some of the FDA's most long-serving members (Robert Temple, Janet Woodcock, John Jenkins) have become, in recent years, more receptive to some industry arguments about drug innovation and the regulation of safety. Since these members have not left for the cozy pastures of the pharmaceutical industry

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<sup>17</sup> Carpenter, Dean Smith, Michael Chernew and A. Mark Fendrick, "Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?" *Health Affairs*, Web Exclusive, December 17, 2003, W3-618-624.

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(and they long ago could have), and since these members have been important catalysts in the agency's changes, it is unlikely that the revolving door accounts for the change. What is more likely, if corrosive capture is involved, is that the political organizations of the global pharmaceutical industry have come to shape the conversation about how drugs ought to be regulated. Chief among these developments is the notion that there is a direct tradeoff between drug safety and drug innovation, and that these values (and not market confidence or scientific improvements in drug quality per se) are the main variables to be considered in examining this regime of regulation.<sup>18</sup>

To the extent that cultural capture embodies a change in regulatory cognition, there are seasoned observers of American pharmaceutical regulation who believe that it has occurred. In January 2010, Jim Dickinson, editor of *FDA Webview* and a long-time columnist and consultant on matters in the pharmaceutical sphere, remarked that the FDA was more “pro-industry” than at any time in the previous 35 years, and that new Obama Administration appointees Margaret Hamburg (Commissioner) and Joshua Sharfstein (then Principal Deputy Commissioner) could do little to change this fact, because the mechanism was embedded in agency culture. In a widely read post on his web log in 2010, Dickinson wrote that

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<sup>18</sup> It is here where I must myself offer something of a *mea culpa*, as some of my own early work on FDA pharmaceutical regulation contributed to the reification of this tradeoff. “Groups, the Media, Agency Waiting Costs, and FDA Drug Approval,” *American Journal of Political Science* 46 (2) (July 2002): 490-505; “The Political Economy of FDA Drug Approval: Processing, Politics and Implications for Policy,” *Health Affairs* 23 (1) (January/February 2004): 52-63. In more recent writings – *Reputation and Power* (2010) – and I have tried to incorporate other variables that have eluded much of the public and academic conversation.

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It has taken almost a generation, but by now, the pro-industry infiltration of FDA's culture is firmly entrenched. Not only is collaboration in product reviews officially encouraged, but good relationships across the regulatory fence hold the prospect of a possible future career in a well-paid industry job - a connection that is less likely to be publicly noticed in news media that now have to line up for information that has been filtered through agency press offices. The arm's-length relationship that formerly ruled every contact between agency and industry has become a fading memory.

According to health care journalist Merrill Goozner, Dickinson argued that “the shift in culture accelerated after the 1992 passage of the Prescription Drug User Fee Act, which made the agency dependent on industry funding.” He concludes there's nothing that Margaret Hamburg, the new commissioner, and Joshua Sharfstein, her deputy, can do about it.” Dickinson then quoted a former FDA chief of enforcement, who wrote that: “User fees at FDA are the primary villain, because they “allowed the industry to dictate the changes at the FDA in programs, procedures and practices. It will be impossible for the Obama administration to reverse the trend because as long as the user fees are in place the industry has the upper hand.”<sup>19</sup>

Coming from an observer with the knowledge of Dickinson, these are strong words and even stronger quotations. They certainly compel us to entertain the possibility of regulatory corrosion through cultural capture. Yet as plausible as that case may be, plausibility lies a far distance from proof. This distance, in general, is a problem with cultural capture accounts; not unlike the kind of hegemony postulated by the Italian theorist Antonio Gramsci, it is difficult to follow the train of concepts and thoughts from their source in industry to their realization in the

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<sup>19</sup> The Dickinson language, reproduced in a Health Care blog column by Goozner, appears at <http://www.reducedrugprices.org/read.asp?news=4978> (accessed July 16, 2011).

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minds and actions of regulatory officials. It is also difficult to evaluate the necessary counterfactuals – in the absence of cultural capture, would capture have occurred anyway? Would regulatory officials have come to these conclusions in the absence of industry pressure and dialogue? – in these claims. Still, one lesson from recent evidence, including the plausibility of cultural capture of the FDA, is clear; the capture being entertained is not of the Huntington-Bernstein-Stigler sort of constructed entry barriers, but of the corrosive sort whereby deregulation is plausibly being accomplished through non-legislative means.

### **Pharmaceutical Regulation: A Review of Statistical Evidence**

While the historical evidence offers a clear rejection of industry capture hypotheses for American pharmaceutical regulation, it is important to consider aggregate statistical evidence from regulatory operations. Here, too, the evidence allows for strong rejection of Stiglerian capture hypotheses, even as we observe some correlations that, initially, would seem to cohere with capture accounts.

#### Firm Sales Regressions

One illuminating test of entry-barrier capture for a regulatory agency like the FDA can be applied to its approval decisions. Since regulatory approval is required for market entry, one might surmise that larger firms are likely to pass through this process more quickly than smaller firms, especially if the regime is rigged against smaller and newer competitors. An important operationalization of this hypothesis is that larger and wealthier firms should receive quicker review times. The data for the present analysis of this hypothesis consist of 447 new molecular

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entities (NMEs) submitted to the FDA over the period 1979 to 2000.<sup>20</sup> A larger set of drugs was submitted, but the sample here contains verifiable review time data, and available firm data such as submission histories, sales and the like. During this period, the FDA reported that approximately 25% of all NDAs are not (eventually) approved (FDA 1988), so the present sample may over-sample or under-sample non-approved drugs, depending upon the analysis.<sup>21</sup> All NMEs in our analysis were considered under the FDA's new drug application (NDA) procedures, but not all NDAs during this period are included in our sample. In particular, generic drug applications, supplemental indication submissions which occur when a company seeks to market its drug for a disease other than the one for which it was originally submitted, and abbreviated new drug applications (ANDAs) are excluded from analysis. The dependent variable is the review time, in months, from the NDA submission date to the NDA approval date (if approval occurred).

Any number of pharmaceutical firms may combine to develop and market a drug. One firm may discover the chemical entity, license it another for clinical development in return for

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<sup>20</sup> Some of the analysis conducted here was conducted for a broader, not yet published paper entitled "Why Do Bigger Firms Receive Faster Drug Approvals?" co-authored with Colin Moore, Marc Turenne, Ian Yohai and Evan James Zucker.

<sup>21</sup> Acquiring complete data for non-approved drugs is a very difficult undertaking. The essential dilemma is that any and all information concerning an NDA that is not yet approved is considered proprietary under FDA regulations and is excluded from availability under the Freedom of Information Act. In fact, the FDA is legally proscribed from acknowledging the *existence* of a pending NDA until (and only if) the application is approved. In the 1960s, medical reporters reported that approximately "30% of all applications are withdrawn or die as incomplete. Formal rejection is rare." "Safety and skepticism: thalidomide," *Modern Medicine*, October 15, 1962, p. 28.

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up-front and “milestone” payments, and then the drug may be marketed by yet a third company. Almost invariably only one of these firms sponsors a new drug application to the FDA. All of the firm-level measures used here are keyed to the *submitting firm*. In most cases, the submitting firm has played an important role in the clinical development of the drug (funding clinical trials, for example) even if the firm in question did not discover the chemical entity (Carpenter 2010, chapter 10).

*Measuring Firm Size.* I use several indices to measure the size of firms. I first use world sales in the year of the drug’s submission. World sales are preferable to U.S. sales because pharmaceutical revenues can come from a variety of national markets. I calibrate each firm’s sales to a common index (U.S. dollars) using average yearly exchange rates, then deflate the dollar aggregates using implicit GDP price deflators. Occasionally, I also use firm-specific employment aggregates, as larger firms will customarily employ more workers. These workers may represent a political constituency – e.g., the “Pill Belt” commonly understood to comprise New Jersey, Eastern Pennsylvania, Delaware and Maryland – that politicians may seek to satisfy by lobbying the FDA.

*Measuring Familiarity: Submissions and Mergers.* For each drug submitted, I tabulate the number of previous submissions that the submitting firm has *at the date of NDA submission*. Because the sample may not capture all non-approved drugs, my measure probably underrepresents firm submissions. For firms that merged during our sample period, we restart this counter but also code for the merger with a dummy variable and a separate variable

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tabulating the years since the firm's most recent merger. Mergers may lead to greater FDA uncertainty over firm attributes; they combine the experience of two or more firms but also generate a "matching" effect about which the agency must learn.

[Table 3 about here.]

*U.S. versus non-U.S. firms.* Rent-seeking would predict that domestic firms will be privileged over foreign ones, at the very least not disadvantaged relative to foreign firms. One would particularly expect this pattern in U.S. pharmaceutical regulation, given the FDA's putative history of being more danger-averse than regulators overseas (Grabowski and Vernon 1983) and the cohesive political organization of pharmaceutical manufacturers here. Yet the estimates show that, *in the aggregate, it is foreign firms who pass more quickly through the FDA's drug review process in the 1979 to 2000 period.* This is a direct and strong refutation of Stiglerian capture theory.

The rejection of rent-seeking and capture hypotheses may seem odd, given that wealthier and larger firms do seem to bear approval time advantages. Yet when one turns to explain large-firm advantage at the FDA, the results here are remarkably inconsistent with the most basic predictions of rent-seeking theory. Domestic firms do much worse than foreign firms in FDA regulation, and older firms do worse than younger ones. Analyses of lobbying contributions, moreover, show inconsistent results that disappear once other covariates are added to estimation.

The analyses show that, once the effect of mergers is accounted for, the simple advantage of being better known to the agency accounts for as much as 55% of estimated large-firm advantage in

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NDA approval times. Adding this variable and controlling for firm fixed effects is enough to make the estimated effect “disappear” in the sense of falling below conventional levels of statistical significance (Table 2).

In related analyses of review times,<sup>22</sup> the relationship between order-of-entry into a market niche (the particular disease being treated by the drug) and review times was examined. Again, entry-barrier capture accounts such as the Huntington-Bernstein-Stigler synthesis suggest that earlier entrants to a market niche should receive quicker and steadier regulatory approval. This relationship was indeed discovered, yet analysis of the data (tied to mathematical modeling) suggests that the reason for “early-entrant protection” in FDA drug review was not industry capture, but patient advocacy. Once the first few drugs for a disease had been introduced on the market, the pressure for additional approvals fell sharply, as patients and their advocates become politically “satisfied” with the supply of new drugs available and their propensity to lobby for more approvals falls.

One must acknowledge, in presenting and reviewing this evidence, the very real possibility that capture and rent-seeking may express themselves in other venues, namely the ability of the FDA to induce pre-NDA product abandonment through rulemaking and expectations of delay at the NDA review stage. These hypotheses remain untested, and the proper framework for doing so remains one which submissions are endogenous to the review process, both theoretically (Carpenter

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<sup>22</sup> Carpenter, Susan Moffitt, Colin Moore, Ryan Rynbrandt, Michael Ting, Ian Yohai, and Evan James Zucker), “Early-Entrant Protection in Approval Regulation: Theory and Evidence from FDA Drug Review,” *Journal of Law, Economics and Organization*, 26 (2) (Fall 2010) [e-published April 2009 at doi: 10.1093/jleo/ewp002].

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and Ting 2007) and empirically, through joint estimation of a submission equation and an approval equation. The present paper, we hope, has clarified what the sample ought to look like (it need include non-approved drugs), has elucidated the importance of firm reputations and disease politics, and has clarified the behavior of the FDA, the last mover in the complicated game of drug development.

### **Related Considerations and Conclusion**

Although the present analysis has been focused upon pharmaceuticals, it is useful to consider related commodities where the FDA and the U.S. government have been slow to assert their authority. Consider the following two product types, both of which deserve more academic study, but where a cursory look at their regulation suggests a

- *Nutritional supplements and dietary supplements*: public health advocates and some FDA officials have long tried to regulate dietary supplements, which by their classification as foods have escaped the gatekeeping provisions of the 1938 and 1962 legislation governing new drugs. An entry-barrier approach to capture would suggest that the pharmaceutical industry would attempt to get these drugs regulated, as their relatively large market likely substitutes for a considerable amount of pharmaceutical utilization and sales. Yet repeated attempts by the FDA and Congress to regulate the dietary supplements industry have failed; in some cases (as with the Proxmire Amendment of 1976 and the *Dietary Supplement Health and Education Act* of 1994 (DSHEA), these attempts have

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been so heavily rebuffed that the FDA's authority over these products has been rigidly delimited or even prohibited.

- *Medical devices*: given that the pharmaceutical industry has a longer history than the medical device industry, and that surgical procedures and medical devices compete with pharmaceuticals for the treatment of disease, one would plausibly expect, under an entry-barrier capture account, that drug companies would use the approval process to erect barriers to entry among devices. Yet most observers of the medical device industry and the pharmaceutical industry over the past thirty years would argue that it is the medical device industry which is more lightly regulated as to approval, which is the reverse of what an entry-barrier capture perspective would suggest. Some of these apparent differences concern FDA behavior, whereas others derive from legislative sources such as the Medical Device Amendments Act of 1976 and related rulemaking.

The strongest conclusion that can be drawn from the historical and statistical evidence is that entry-barrier capture of the sort theorized by Huntington, Bernstein and Stigler is not a solid or powerful explanation for the development or operation of American pharmaceutical regulation. If anything, the capture that has plausibly occurred has been of the corrosive, deregulatory kind, and this raises larger questions about the limits of existing capture theory.

To the extent that capture exists in American pharmaceutical regulation, it is certainly weak capture and not strong capture as we have defined it in this volume. Some corrosion may have occurred – although the evidence supporting these vague claims is impressionary and far from

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robust – and yet, the plausible corrosion functions much like the exception that proves the rule. The decline in trust in the FDA has corresponded with a decline in trust in the pharmaceutical industry and its new products,<sup>23</sup> and this relationship underscores the critically valuable confidence benefits that approval regulation of new drug treatments brings.

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<sup>23</sup> Carpenter, *Reputation and Power*, chapter 12, and Alex Berenson, "Big Drug Makers See Sales Decline with their Image," *New York Times*, November 14, 2005.

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Table 1: Probit Analyses of Three Votes on S.5.			
[Senate Votes, 74 <sup>th</sup> Congress]			
Variable	S. 5 Amendment Reconsideration [4/1/1935]	S. 5 Amendment Reconsideration [4/2/1935]	Bailey Amendment [4/8/1935]
Constant	1.8371 (1.5636)	<b>3.8839</b> (1.8262)	-1.7690 (1.4917)
D-NOMINATE 1-D	<b>-2.0944</b> (0.8531)	<b>-2.6960</b> (1.0643)	<b>1.8166</b> (0.8019)
D-NOMINATE 2-D	-1.3916 (0.8194)	0.3583 (1.1096)	0.3844 (0.8613)
Party (Democrat = 1)	-0.7572 (0.6857)	-1.3627 (0.8369)	1.0947 (0.6750)
Percentage of State Vote for FDR, 1932	-0.0041 (0.0206)	0.0169 (0.0250)	0.0081 (0.0185)
Change in % of State for FDR, 1932-1936	-0.0103 (0.0321)	-0.0471 (0.0386)	-0.0177 (0.0250)
% of State Population African- American	-0.0445 (0.0396)	-0.0429 (0.0492)	0.0153 (0.0377)

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% of State Population Illiterate	-0.1166 (0.0790)	<b>-0.2109</b> (0.0924)	0.1061 (0.0818)
% of State Population Educated	-0.0879 (0.0494)	<b>-0.2119</b> (0.0683)	0.0370 (0.0469)
% of State “Gainful Workers” Unemployed	<b>0.4181</b> (0.1327)	<b>0.5893</b> (0.1736)	-0.0815 (0.1134)
Retail Sales as % of Wholesale	-0.0010 (0.0026)	-0.0009 (0.0028)	-0.0007 (0.0025)
South	<b>2.1259</b> (0.9639)	1.1556 (1.5649)	-0.8767 (0.8770)
Number of Proprietary Association firms in state	0.0375 (0.0215)	0.0311 (0.0245)	-0.0179 (0.0178)
Number of UMMA firms in state	<b>-0.2596</b> (0.0829)	<b>-0.2888</b> (0.0929)	0.0882 (0.0541)
<i>N</i> (df)	83 (69)	75 (61)	81 (67)
LLF	-43.512	-33.796	-49.307
Pseudo-R <sup>2</sup>	0.2417	0.3396	0.1139

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Notes: Asymptotic standard errors in parentheses. Bold coefficient estimate implies statistical significance at  $p < 0.05$  (two-tailed test). UMMA firms and Par firms variables correlated at 0.5598. Removal of UMMA firms variable results in negative but insignificant estimate on PA firms variable.

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Table 2: Duration Regressions for New Molecular Entities, 1979-2000

[Negative coefficients imply association with faster reviews.]

(Model)	(1)	(2)	(3)	(4)
	No Fixed	Firm Fixed	No Fixed	Firm Fixed
VARIABLES	Effects	Effects	Effects	Effects
ln(firm sales)	<b>-0.0757</b>	<b>-0.0511</b>	<b>-0.0587</b>	-0.0203
	(0.0147)	(0.0213)	(0.0181)	(0.0216)
ln(firm submissions)			-0.0728	<b>-0.3705</b>
			(0.0458)	(0.0746)
Constant	3.4623	3.4518	3.4434	3.4746
	(0.1263)	(0.1283)	(0.1263)	(0.1247)
NDA's	447	447	447	447
Number of disease-based	149	149	149	149
random effects				

Log-normal duration regressions of FDA review time on firm sales and firm previous submissions at time of submission. Standard errors in parentheses; all tests are two-tailed.

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Table 3: Table 2: Duration Regressions for New Molecular Entities, 1979-2000

[Negative coefficients imply association with faster reviews.]

(Model)	(1)	(2)
VARIABLES		
ln(firm sales)	-0.0447 (0.0202)	-0.0381 (0.0201)
ln(firm submissions)	-0.0945 (0.0485)	-0.1071 (0.0510)
Foreign Firm	-0.1508 (0.0855)	-0.1296 (0.0861)
Merged Firm		-0.3475 (0.2081)
ln(submissions) merged	*	0.1027 (0.1067)
Constant	3.4449 (0.1294)	3.4351 (0.1291)

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NDA	439	439
Number of disease-based random effects	148	148

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Log-normal duration regressions of FDA review time on firm sales and firm previous submissions at time of submission. Standard errors in parentheses; all tests are two-tailed

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