Regulator Heterogeneity and Endogenous Efforts to Close the Information Asymmetry Gap

Jeffrey T. Macher *Georgetown University*
John W. Mayo *Georgetown University*
Jack A. Nickerson *Washington University in St. Louis*

Abstract

The now standard principal-agent model of regulator-firm interactions typically assumes the presence of a single regulator and an exogenously determined information asymmetry between the principal and the agent. In this paper we draw upon a unique data set of regulatory inspections conducted by the U.S. Food and Drug Administration (FDA) to explore the consistency of these assumptions with the actual practice of regulators. We find that the canonical assumptions of the agency paradigm are strained by, if not altogether inconsistent with, the key practical realities of regulation by the FDA. Our analysis uncovers several dimensions along which regulators actively and endogenously seek to close the information asymmetry gap. We also find considerable regulator heterogeneity, which in turn depends in part upon the specific training and experience of individual regulators.

1. Introduction

Government regulation consists of a set of rules with which regulated entities must, under threat of penalty, comply. Early economic models of regulation assumed consequently that regulatory rules were sufficiently well specified and binding that neither regulators nor the firms they regulate had discretion in enforcing or adhering to these regulations. In the past 2 decades, however, econ-

This research was supported in part by funding from the Georgetown Center for Business and Public Policy in the McDonough School of Business, Georgetown University, and from the Center for Research in Economics and Strategy and the Boeing Center for Technology and Information Management at the Olin School of Business, Washington University in St. Louis. We thank Chris Borek, Brad Jensen, Tom Lyon, Dennis Quinn, Rob Shapiro, Jim Wade, Scott Wallsten, and seminar participants at Georgetown University for helpful comments on earlier drafts.

[*Journal of Law and Economics*, vol. 54 (February 2011)]
 0022-2186/2011/5401-0002$10.00

omists have come to recognize that this tight theoretical construct fails to hold in a variety of regulatory contexts. For instance, economists now acknowledge that rules in the regulatory contract are commonly and sufficiently ill specified that regulated firms have some (perhaps considerable) discretion in their responses to regulations.[1] Principal-agent models of regulation, which assume information asymmetries between firms and regulators, offer the most common approach to modeling such firm discretion (Laffont and Martimort 2002). Central to these models has been the assumption that regulators are underendowed with information regarding the operating technology (typically, costs or quality) of the regulated firm. This assumption of information asymmetry has, in turn, evoked a large and growing literature on the design of optimal regulatory mechanisms that seeks to align the interests of regulators (generally assumed to be welfare maximizing) and the firms they regulate (Baron 1989; Armstrong and Sappington 2007).

While the literature on optimal regulatory design has significantly advanced understanding of economic regulation, it is less than satisfying on at least three grounds. First, research on optimal regulatory design mechanisms has generated considerable theoretical discussion, but the actual implementation of these schemes is rare.[2] As a practical matter, this result may spring from the significant (costly) changes to existing regulatory mechanisms that would be necessary to implement these optimal designs. Thus, despite providing aspirational benchmarks, these design mechanisms may be of more theoretical than practical importance.

Second, models of optimal regulatory design routinely begin with the assumption of an exogenously generated and immutable information asymmetry.[3] Within this setting, identical rational firms (the agents) possess private information about their actions and seek either to maximize profit by enjoying discretion in the extent to which they meet regulatory guidelines (thereby earning information rents) or to gain favorable treatment by providing benefits to the regulator. In practice, however, regulators may undertake activities to close the information asymmetry gap. The assumption of an exogenous and immutable information asymmetry is in this sense not congruent with the practical efforts made by regulators to overcome this asymmetry. Thus, while regulators expend considerable effort in managing and reducing information asymmetries, the sub-

[1] Beyond the more obvious situations in which firms discretionarily choose to fail to comply with a regulatory standard, recent literature examines situations in which firms discretionarily engage in costly activities to more than comply with regulatory constraints. See, for example, Weil (1996), Maxwell, Lyon, and Hackett (2000), and King and Lennox (2000).

[2] Even the most notable shift of regulatory design instruments—from rate-of-return regulation to price-cap regulation in traditional public utility industries—is far from complete (Blank and Mayo 2009). Numerous other incentive-compatible regulatory schemes have received even less attention in actual practice. For instance, compare the regulatory mechanisms reviewed in Armstrong and Sappington (2007) with those actually adopted in practice.

[3] See Baron and Besanko (1984, 1987) and Khalil (1997) for notable exceptions.

stantial thrust of the modeling attention to this point has been aimed at regulatory redesign to promote incentive compatibility between the principal and the agent.

Third, in a variety of regulated industries, the common modeling assumption of a single, homogeneous regulator is inapt. Many regulatory agencies, including the Occupational Safety and Health Administration (OSHA), the Nuclear Regulatory Commission (NRC), and the Food and Drug Administration (FDA), comprise hundreds of regulatory foot soldiers. These armies of regulators are the individuals who visit firms and facilities, implement complex regulations, determine and report violations, and expend effort to overcome asymmetric information. If we relax the assumption of a single regulator and allow for the potential of boundedly rational enforcement by these regulatory foot soldiers, the possibility of significant regulator heterogeneity obtains. If regulators are not homogeneous but instead boundedly rational as reflected by heterogeneous endowments of human capital, then several new questions are introduced into the theory and practice of regulation. In particular, the current emphasis on the design of optimal regulatory mechanisms in the face of exogenous information asymmetries gives way to concerns about human capital development and management and organizational incentives and structures, as these factors become more important features of the regulatory landscape.[4]

To probe the dimensions of these underexplored features of regulation, we focus on regulators in the context of the FDA. We chose the FDA because it has a substantial economic impact in and on the U.S. health care system and has structural features that are similar to those of other regulatory agencies. Like OSHA, the NRC, and many other state and federal regulatory agencies, the FDA comprises hundreds of individual investigators. We also have unprecedented access to data within a division of the FDA—the Center for Drug Evaluation and Research—that is in charge of oversight and regulation of pharmaceutical drug products.[5] Our sample represents a comprehensive 14-year (1990–2003) panel data set of every inspection undertaken by more than 700 investigators at more than 2,400 pharmaceutical manufacturing facilities around the world.

Within this regulatory context we explore two core assumptions of the canonical principal-agent framework. First, we probe the exogeneity assumption regarding the information asymmetry gap between the principal (here, the FDA) and the agents (here, the pharmaceutical manufacturing facilities) it regulates. Specifically, we explore the extent to which FDA inspection decisions are exogenous in the sense that they are unaffected by information about the focal manufacturing facility. Second, the assumption of a single, monolithic principal (the regulator) is rather obviously violated in the context of the FDA. Whether

[4] See Fremeth and Holburn (forthcoming) for an examination of the effects of regulator experience, management, and organization on reducing information asymmetries and, thereby, reducing regulators' decision costs and facilitating policy making.

[5] Two of the authors are Food and Drug Administration (FDA) special government employees. Working in this capacity, we have secured both extraordinarily granular and extensive data on the internal operations and external performance of this agency.

violation of this assumption is consequential or inconsequential for understanding regulatory outcomes depends upon the extent to which regulators, on the whole, are approximately similar (that is, uniform) in their behaviors. We accordingly explore the extent to which regulators' decisions are rational and uniform. The natural counterhypothesis is that these foot soldiers enjoy only limited human capital, are boundedly rational, and display significant heterogeneity in their regulatory decision making. In short, we seek to understand what possibilities exist and how effective these possibilities might be in practice for regulators to overcome the much-ballyhooed information asymmetry gap that has become a central part of our understanding of regulation.

Our empirical analysis examines two central regulatory decisions regarding the manufacture of pharmaceutical drug products. The first is whether and when to inspect a pharmaceutical manufacturing facility. Implementing several hazard-rate models, we estimate how frequently the regulatory agency chooses to inspect a given manufacturing facility. Our analysis indicates that the FDA chooses inspection sites endogenously, drawing on information provided from prior inspections and compliance outcomes to manage decisions of whether and when to conduct inspections. The second regulatory decision is whether or not, upon inspection, to find a manufacturing facility compliant. This analysis again indicates that regulators draw significant information from prior performance to establish heuristic impressions of manufacturing facilities' compliance propensities. The reputations of the facilities being inspected, which stem from the information provided to regulators from past inspections, are shown to alter regulatory outcomes significantly.

Our analysis of regulatory outcomes also reveals substantial heterogeneity in regulators, with significant differences across FDA investigators in the propensity to find manufacturing facilities in violation of regulatory standards.[6] We find that investigator training and experience are critical determinants in generating regulatory heterogeneity. But even after accounting for idiosyncratic variations in both investigator- and inspection-specific characteristics, as well as a variety of manufacturing-facility-specific characteristics, we also find pronounced evidence of regulator heterogeneity. Ceteris paribus, some investigators are 40 percent more likely than the median investigator to impose sanctions on manufacturing facilities, while other investigators are 20 percent less likely to do so. In both empirical undertakings, we find that the canonical assumptions of the agency paradigm are strained by, if not altogether inconsistent with, the key practical realities of regulation by the FDA.

Our study provides several new insights on the economic theory of regulation. While previous research has focused on the theoretical potential for regulatory redesigns to overcome the information asymmetry problems, we find tangible evidence on the part of regulators to mitigate this gap within a given regulatory design. We also find strong evidence of a clear and consistent empirical regularity:

[6] See Feinstein (1989, 1990) for earlier empirical examinations of regulator heterogeneity.

substantial variation by investigator exists in regulatory outcomes. Regulator heterogeneity is thus a tangible and significant empirical phenomenon that needs to be considered in the modeling and design of regulatory mechanisms. Moreover, our study identifies several sources of regulator heterogeneity. Regulatory outcomes appear to depend on the amount and type of training investigators receive and the frequency with which investigators participate in inspections, as well as other unobserved investigator-specific factors. These findings provide strong evidence that regulatory outcomes can and do depend on the level of the accumulated idiosyncratic knowledge of an investigator. We therefore confirm the often-assumed information asymmetry gap. Nevertheless, this information asymmetry is not entirely consistent with the uniform gap assumed in the literature, as we find strong evidence of heterogeneity in human capital across individual inspectors. This latter finding points toward an endogenous dimension of the information asymmetry gap and thereby reveals a new tool with which economists may better design and regulators may more adroitly implement efficient regulatory policies.

2. Background

Early models of the regulatory process incorporated an exogenous set of regulatory constraints on firms by consumer- or total-surplus-maximizing regulators (Averch and Johnson 1962). Over time, these models have given way to more sophisticated perspectives that allow regulated firms to possess knowledge of their production processes (for example, costs or quality) to which regulators are not, without resource expenditures, privy. Incorporating such asymmetric information in economic models of regulation creates a regulatory game. On the one hand, firms have discretion in the extent to which they comply with regulatory standards because of their idiosyncratic and embedded information. On the other hand, regulators seek to design regulatory mechanisms to elicit (consumer- or total-) surplus-maximizing behavior by regulated firms, fully aware that they are underendowed with information. If first-best mechanisms can be found, then no regulatory monitoring is necessary and there is no unanticipated discretionary behavior on the part of firms (Armstrong and Sappington 2007).

In the absence of a first-best incentive mechanism, however, regulatory monitoring offers an alternative mechanism to mitigate firm discretion. If monitoring is costless, detection of violations is complete, and regulators are unbounded by the extent of fines they may impose, then any initial information asymmetries enjoyed by firms can be overcome and regulatory noncompliance ended. In reality, inspections are costly, detection is not perfect, and fines are bounded. Regulators thus face the challenge of overcoming information asymmetries by deciding whether or not to inspect a given firm and how much to invest in

detection efforts. These issues are the focus of our empirical model of FDA regulation.

The FDA is an agency of the U.S. Department of Health and Human Services responsible for regulating food, dietary supplements, drug (pharmaceutical and biological) products, blood products, medical and radiation-emitting devices, veterinary products, and cosmetics in the United States. As a federal regulatory agency, the FDA has mandated goals of ensuring the safety of the general public and the effectiveness of marketed products that fall under its regulatory umbrella.

The FDA is organized into six centers with separate responsibilities related to health and safety, depending upon the product or end user.[7] The Office of Regulatory Affairs (ORA) oversees the general regulatory affairs for each center. We examine the regulation of pharmaceutical drug products that fall under the Center of Drug Evaluation and Research (CDER). The CDER seeks to ensure that medicinal drug products used for the treatment and prevention of diseases are proven safe and effective before they are used by patients. Among its many duties, the CDER regulates the introduction of new drug products and the manufacture and distribution of approved drug products. Our focus is on the latter (the regulation of pharmaceutical manufacturing) as opposed to the former (the review and approval of new drug molecules, or drug development).

The FDA is required by the Federal Food, Drug, and Cosmetic Act of 1938 (21 U.S.C. sec. 301) to inspect all registered manufacturing facilities that sell drug products within the United States, regardless of the facilities' physical location. Federal statutes mandate that pharmaceutical firms manufacturing drug products for human administration operate under compliance standards termed current good manufacturing practices (referred to as cGMPs), which require that all drug products (finished dosage forms) and drug components (bulk and active pharmaceutical ingredients) be in conformance with guidelines related to safety and have "the identity, strength, quality and purity that they purport or are represented to possess" (Mathieu 2000, p. 335).

Since establishing cGMP requirements in 1962, the FDA has taken a general regulatory approach whereby only broad guidelines related to cGMP compliance are provided to pharmaceutical firms. Supplementary information—referred to as "guidances"—provides additional specificity only when necessary and normally around requirements related to manufacturing, quality control and documentation, or updates for process and methods validation. The FDA targets and seeks to maintain cGMP compliance around the concept of quality assurance such that (1) quality, safety, and effectiveness must be designed and built into drug products, (2) quality cannot be inspected or tested into finished products, and (3) each step of the manufacturing process must be controlled to maximize the likelihood that finished drug products are safe and efficacious (Mathieu 2000).

[7] These six centers are (1) the Center for Food Safety and Applied Nutrition, (2) the Center for Drug Evaluation and Research, (3) the Center for Biologics Evaluation and Research, (4) the Center for Veterinary Medicine, (5) the Center for Devices and Radiological Health, and (6) the National Center for Toxicological Research.

The cGMP regulations seek to ensure the quality of drugs by setting minimum standards for all manufacturing facilities in 10 separate areas (Mathieu 2000),[8] which apply to both approved drug products sold commercially and experimental drug products operating under new drug application status.

The FDA implements an active cGMP compliance and enforcement program. The ORA sets the overall enforcement budget and is the organizational unit in which most investigators are housed. Twenty FDA district offices have inspection and enforcement responsibility for domestic manufacturing facilities, while the ORA and the CDER share responsibility for international manufacturing facilities. From one to several FDA investigators take part in individual cGMP inspections, depending upon the type of manufacturing facility and types of compounds manufactured. Investigators generally have wide latitude in conducting cGMP inspections around the 10 areas mentioned above.

After a cGMP inspection, manufacturing facilities are notified as to any violations. Formal inspection outcomes determine whether the manufacturing facility is in or out of cGMP compliance—the latter requiring some response on the part of the manufacturing facility. Minor cGMP violations generally fall under the responsibility of the FDA district office that conducted the original inspection. A period of time in which to address and correct violations is provided to manufacturing facilities before additional regulatory actions are taken. If outstanding violations are left unaddressed, however, the FDA can and does escalate the severity of penalties, including but not limited to legal sanctions (such as fines, product seizures, injunctions, and prosecutions), controlled distribution, and/or limited marketing. The FDA proposes such regulatory actions to the U.S. Justice Department and files cases with U.S. district courts if and when necessary.

3. Empirical Estimation

3.1. Econometric Models

In the absence of perfect and costless monitoring, pharmaceutical manufacturing facilities may be expected to earn rents on information asymmetries through the shirking of sound manufacturing practices. The size of any such rents is determined by whether, and the extent to which, regulators undertake efforts to overcome information asymmetries. Accordingly, we turn to two complementary empirical examinations of the efforts that the FDA makes in the face of these information asymmetries. We first examine agency-level efforts that manifest in decisions on how frequently to inspect particular manufacturing facilities. We then turn to a more granular examination of the determinants of regulatory inspection outcomes. We explore in particular whether characteristics of the inspection process or those of the individual FDA regulator—including

[8] These areas are (1) organization and personnel, (2) building and facilities, (3) equipment, (4) control of components and drug product containers and closures, (5) product and process controls, (6) packaging and labeling controls, (7) holding and distribution, (8) laboratory controls, (9) records and reports, and (10) returned and salvaged drug products.

training and experience levels—affect regulatory outcomes, after controlling for other factors related to the manufacturing facility and the FDA inspection process.

3.1.1. Risk-of-Inspection Analysis

Given the associated costs, pharmaceutical manufacturing facilities should exhibit heterogeneity with respect to cGMP regulatory compliance. Indeed, over our entire 14-year sample, only 18 percent of manufacturing facilities inspected are found to be in compliance in any 2-year window, while the remaining 82 percent of manufacturing facilities have at least one (either minor or major) cGMP violation in any 2-year window.

Knowing that some manufacturing facilities are more likely to be compliant and others are less likely, but with limited knowledge ex ante of which facilities fall into either category, the FDA faces a first-tier information asymmetry gap—namely, determining which manufacturing facilities to inspect and when. While the FDA may be seen to nominally accomplish its goal of promoting cGMP compliance through a system of random inspections, it is also likely that in making inspection selection decisions the agency draws inferences from prior inspections of manufacturing facilities. To investigate this possibility, we use event history analysis to explore the factors that influence whether and when the FDA chooses to inspect manufacturing facilities. We model the time between regulatory inspections of drug manufacturing facilities as a stochastic process, defining the transition rate $r(t)$ from no inspection to inspection for a pharmaceutical manufacturing facility j at time t as

$$r_j(t) = \lim_{t' \to t} \frac{\Pr(t \leq t' \mid T \geq t')}{t' \to t}.$$

We estimate models that specify the transition (or hazard rate) as a function of time t and a vector of covariates $\boldsymbol{Z}$ that represents our independent variables. This estimation approach takes the general form $r_j(t) = f(t, \boldsymbol{Z}_{jt})$. We employ three separate hazard models—exponential, Gompertz, and Cox proportional—in order to explore to what extent assumptions about the hazard rate function affect our estimation results. The exponential model can be parameterized as either a proportional hazards or an accelerated failure time model and is suitable for modeling data with a constant hazard rate. The Gompertz model is parameterized as a proportional hazards model and is suitable for modeling data with monotone hazard rates that either increase or decrease exponentially with time. The Cox proportional model is parameterized as a proportional hazards model but makes no assumptions about the baseline hazard. As our measures represent the hazard of manufacturing facility inspection, variables that lead to shorter (longer) times between inspections have positive (negative) coefficients.

3.1.2. Inspection Outcome Analysis

Given that a decision to inspect a particular manufacturing facility has been made, the FDA faces a second-tier information asymmetry gap. In particular,

the possibility arises that an individual FDA investigator's characteristics (for example, training and experience level) influence cGMP compliance decisions. We accordingly model the relationship between individual investigator characteristics and the likelihood of noncompliant cGMP outcomes. We anticipate that the unobserved probability of a manufacturing facility's being found cGMP noncompliant ($cGMP^{\star}_{ijt}$) depends upon a vector of variables related to the experience and training levels of the individual investigator ($\boldsymbol{I}_{ijt}$) as well as a vector of other independent and control variables ($\boldsymbol{X}_{ijt}$):

$$cGMP^{\star}_{ijt} = \boldsymbol{\beta}_0 + \sum \boldsymbol{\beta} \boldsymbol{I}_{ijt} + \sum \boldsymbol{\gamma} \boldsymbol{X}_{ijt} + \mu_{ijt},$$

where β_0 is a constant term, $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are parameter vectors, and μ_{ijt} is a random error term.[9]

Because we do not observe this probability directly, we necessarily draw upon tangible outcomes of inspections. The outcome of any given cGMP inspection i of manufacturing facility j at time t ($cGMP_{ijt}$) results in the facility's being found either in compliance with or in violation of cGMP standards. The observed outcome can reasonably be linked to the underlying unobservable probability as

$$cGMP_{ijt} = \begin{cases} 1 & \text{if } cGMP^{\star} > 0 \\ 0 & \text{otherwise.} \end{cases}$$

Given the categorical nature of the dependent variables, logit or probit is the most appropriate estimation approach. We use the probit model with its underlying assumption of a normally distributed error term using maximum likelihood estimation (results from a logit model are nearly identical). We also examine multinomial logit and ordered probit models to explore whether differences or orderings exist among inspection outcomes in Section 3.5.3.

3.2. Data

Data were obtained directly from the FDA and represent inspections of pharmaceutical manufacturing facilities under the responsibility of the CDER. The CDER oversees both the evaluation of new drug products before they are approved to be sold and their safety and efficacy thereafter. The CDER regulates prescription and over-the-counter drug products, as well as brand-name and

[9] As with many multiequation models, the potential arises herein for contemporaneous correlation in the errors that are observed across the equations. In such circumstances, it may be possible to improve the efficiency of the parameter estimates by incorporating this potential into the estimation process itself. In the case at hand, however, such estimations are made prohibitively complicated by the combined presence of a hazard model in the inspection equation and a limited dependent variable in the inspection outcome equation. While we eschew a more complicated estimation method, we recognize the potential efficiency gains from an estimation that explicitly incorporates the potential for linkages across equations through the error structure. As the current estimation yields parameter estimates that are robustly significant across a variety of specifications, our sense is that any efficiency gains from alternative estimation methods are likely to be limited.

generic drug products, in an effort to ensure that the health benefits outweigh the known risks.

Our main data source is the FDA Field Accomplishments and Compliance Tracking System (FACTS) database, which provides information on completed inspections of domestic and foreign manufacturing facilities selling pharmaceutical drug products in the United States. We assembled data on every inspection conducted under the CDER over a 14-year period (1990–2003). The FACTS database includes detailed information on each cGMP inspection, including the date and length of the inspection, characteristics of the manufacturing facility and investigator(s) involved, the FDA district responsible, and the inspection outcome.

Given the number of mergers and acquisitions in the pharmaceutical industry over the time period of the study, it is important to delineate changes in ownership structure. Fortunately, pharmaceutical manufacturing facilities selling drug products within the United States are required to register with the agency. A registration and listing database maintained by the FDA records the pharmaceutical firm (or firms) that owns each manufacturing facility, the location of each manufacturing facility, and the drug products manufactured in each facility, as well as any changes that occur in this information. We created a corporate ownership database for each manufacturing facility using the FDA registration and listing database, correcting for any identifiable mismatches in the registration history records of the manufacturing facilities in our sample.

Working with the FDA, we also assembled a database on the training of all CDER investigators engaged in inspections of pharmaceutical manufacturing facilities before and during our study window. This database tracks all employer-sponsored training in terms of total courses taken and instructional days. This database also tracks the particular courses—deemed by the FDA to be either focal or supplemental (discussed below)—that were completed by each investigator prior to each manufacturing facility inspection.

3.3. Variables

3.3.1. Dependent Variables

Our first dependent variable measures the frequency with which the FDA inspects manufacturing facilities for cGMP compliance. Inspection Frequency represents the number of calendar days between successive cGMP inspections for a given manufacturing facility. Our second dependent variable captures the regulatory outcome of these cGMP inspections. Inspection outcomes range from a certification of complete compliance (No Action Indicated, or NAI), to mild noncompliance (Voluntary Action Indicated, or VAI), and complete noncompliance (Official Action Indicated, or OAI).[10] Each dependent variable represents

[10] Official Action Indicated outcomes commonly include voluntary recalls by manufacturing facilities, but actions and/or sanctions can be more severe. Recommended OAI actions include banning; certification withholding or revocation; citation; civil penalty; disqualification; not approving emer-

a dummy variable equal to one if the relevant inspection outcome obtains, and zero otherwise. Given the qualitative differences between complete compliance, mild noncompliance, and complete noncompliance, we use OAI as our dependent variable in the empirical analysis of inspection outcomes but examine other permutations in our robustness analysis.

3.3.2. Independent Variables

Several FDA-specific factors are likely to affect the frequencies and outcomes of manufacturing facility inspections. One such factor is the reason for cGMP inspection, which falls into one of three distinct categories: (1) surveillance, (2) compliance, and (3) customer complaints. Surveillance inspections relate to a congressional mandate that the FDA conduct "regular and periodic" inspections of existing manufacturing facilities. Surveillance Inspection is a dummy variable equal to one if the reason for inspection is regular and periodic cGMP surveillance, and zero otherwise. Compliance inspections relate to a requirement that manufacturing facilities notify the FDA if and when they establish new manufacturing processes or make any changes to existing manufacturing processes. This notification provides information that we anticipate will be used by the agency to alter inspection priorities. Compliance Inspection is a dummy variable equal to one if the FDA has received such notification from a manufacturing facility, and zero otherwise. Customers (for example, medical establishments) may have access to information that is unavailable to the FDA. A complaint process within the FDA encourages customers and/or consumers to share this information, which in turn allows the FDA to alter inspection priorities. Customer Complaint Inspection is a dummy variable equal to one if the reason for inspection is a customer complaint, and zero otherwise. We anticipate that the frequency of cGMP inspections is higher and the likelihood of cGMP violations is larger in response to compliance inspections and customer complaint inspections than to surveillance inspections (the omitted category in our empirical analysis).

Another factor that likely affects the frequencies and outcomes of cGMP compliance inspections is the geographic location of manufacturing facilities. Manufacturing facilities in the United States are accounted for by regional fixed effects, while foreign inspections are accounted for by a dummy variable. Foreign Inspection is a dummy variable equal to one if the inspection occurs outside the United States, and zero otherwise. The potential for foreign inspections to evoke different inspection patterns or regulatory outcomes stems mainly from two considerations: first, foreign inspections are more costly than those con-

---

gency permits; injunction; license denial, suspension, or revocation; prosecution; provisional listing; recall (initiated by the FDA); recommendation for denial of pending application; recommendation for revocation of approved application; removal from shippers list; seizure and detention; prohibiting use; warning letter; and demand for destruction.

ducted domestically, and second, FDA personnel conducting foreign inspections differ from their domestic counterparts.[11]

In terms of FDA inspection outcomes, the longer the time between cGMP inspections, the greater the information asymmetry gap and the more likely that manufacturing facilities will (consciously or unconsciously) allow their manufacturing processes to atrophy into noncompliance. Days between Inspections represents the natural logarithm of the number of calendar days between successive cGMP inspections at a manufacturing facility and is included in the econometric analysis of inspection outcomes.

We also account for the potential that the FDA uses information secured from prior manufacturing facility inspections to guide future regulatory decision making. We posit that previous manufacturing facility inspections provide information important to the regulator that is helpful in generating a reputation heuristic. We construct variables based on prior inspection outcomes to determine whether manufacturing facilities have developed good or bad reputations for cGMP compliance and whether recent inspections reveal any improvement or deterioration in manufacturing facilities' commitments to cGMP compliance. Good Reputation is a dummy variable equal to one if the manufacturing facility has been either in complete compliance (received an outcome of NAI) or in mild noncompliance (received VAI) in its two most recent inspections, and zero otherwise. Alternatively, Bad Reputation is a dummy variable equal to one if the manufacturing facility has been in complete noncompliance (received OAI) in its two most recent inspections, and zero otherwise.

We also proxy for information provided by changes to reputational status by accounting for whether the manufacturing facility improved or deteriorated in cGMP compliance performance over its two most recent inspections. Improving Reputation is a dummy variable equal to one if the most recent inspection of a manufacturing facility resulted in a finding of either complete compliance (NAI) or mild noncompliance (VAI) following a previous inspection finding of noncompliance (OAI), and zero otherwise. Deteriorating Reputation is a dummy variable equal to one if the most recent inspection resulted in a finding of complete noncompliance (OAI) following a previous inspection finding of either complete compliance (NAI) or mild noncompliance (VAI), and zero otherwise. Improving Reputation represents the omitted category in our empirical analysis. Table 1 provides additional detail on the classification of these reputation variables.

Our FDA investigator variables include training- and experience-related measures, which we argue influence the probability of detecting noncompliance. We use three variables to capture the level of training of individual FDA investigators. Core Courses is a count of the number of core courses that the investigator

[11] Inspections of foreign pharmaceutical manufacturing facilities are normally undertaken by personnel based in the Office of Regulatory Affairs instead of those in the Center for Drug Evaluation and Research.

Table 1
Variable Definitions

Variable	Definition
Control:	
Prescription	Indicates that the facility manufactures prescription drug products
Prompt release	Indicates that the facility manufactures drug products with prompt-release profiles
Extended/delayed release	Indicates that the facility manufactures drug products with extended- or delayed-release profiles
Gel cap	Indicates that the facility manufactures drug products in gel cap dosage forms
Soft gel cap	Indicates that the facility manufactures drug products in soft gel cap dosage forms
Ointment	Indicates that the facility manufactures drug products in ointment dosage forms
Liquid	Indicates that the facility manufactures drug products in liquid dosage forms
Powder	Indicates that the facility manufactures drug products in powder dosage forms
Gas	Indicates that the facility manufactures drug products in gas dosage forms
Parenteral	Indicates that the facility manufactures drug products in parenteral dosage forms
LV parenteral	Indicates that the facility manufactures drug products in large-volume parenteral dosage forms
Aerosol	Indicates that the facility manufactures drug products in aerosol dosage forms
Bulk	Indicates that the facility manufactures drug products in bulk dosage forms
Suppository	Indicates that the facility manufactures drug products in suppository dosage forms
Sterile	Indicates that the facility manufactures sterile drug products
Products	Logged count of the number of distinct drug products the facility manufactures
Independent:	
Good Reputation	Facility received (NAI, NAI), (NAI, VAI), (VAI, NAI), or (VAI, VAI) in the two most recent inspections
Bad Reputation	Facility received (OAI, OAI) in the two most recent inspections
Deteriorating Reputation	Facility received (NAI, OAI) or (VAI, OAI) in the two most recent inspections
Improving Reputation	Facility received (OAI, VAI) or (OAI, NAI) in the two most recent inspections

Note. NAI = no action indicated; VAI = voluntary action indicated; OAI = official action indicated.

completed prior to the focal cGMP inspection. These courses cover broad and general topics related to pharmaceutical manufacturing and are deemed by the FDA to be particularly important for conducting cGMP inspections.[12] Supple-

[12] Five core courses are considered particularly important for FDA investigators in understanding regulations regarding current good manufacturing practices: (1) Basic Drug School, (2) Advanced Drug School, (3) Preapproval Inspections, (4) Active Pharmaceutical Ingredient Manufacturing, and (5) Sterilization.

mental Courses is a count of the number of other courses that the investigator completed prior to the focal cGMP inspection. These courses cover specialty topics in biology, pharmacology, and manufacturing processes, among others. Total Courses is a count of the number of total (core and supplemental) drug courses the FDA investigator completed prior to the focal cGMP inspection and represents our initial measure of training in the econometric analysis. We examine the effects of the core and supplemental courses measures, as well as the nonlinear effects of training via the inclusion of squared terms, in our robustness analysis.

As FDA investigators become more experienced in conducting inspections, they learn by doing. More investigational expertise may lead to superior understanding in detecting and determining whether or not a manufacturing facility is cGMP compliant. Cumulative Inspections represents the natural logarithm of the number of previous cGMP inspections conducted by the FDA investigator prior to the focal cGMP inspection. As with the training variables, we also examine whether any nonlinear effects of experience on inspection outcomes exist in our robustness analysis.

3.3.3. Control Variables

While our primary interest is in how FDA inspection decisions and FDA investigators' experience and training affect inspection frequency and outcomes, we also control for other potential determinants of these outcomes. The FDA views prescription drug products as posing greater public safety and health consequences, should there be manufacturing problems, compared to over-the-counter drug products (FDA 2004). The presence of prescription drug products in manufacturing facilities may therefore represent an important factor in FDA decisions of whether and when to inspect and in investigator decisions of whether to find facilities cGMP compliant.

Several variables are included to capture manufacturing-facility-specific characteristics. Drug products have different release profiles (prompt, extended, or delayed release) associated with their administration, which are dependent upon several technological parameters, including drug solubility, half-life, protein binding, site of absorption, and so on. We control via dummy variables for each release profile that the focal manufacturing facility is capable of producing at the time of inspection. Drug products also differ in terms of physical dosage characteristics, including such factors as appearance, form, administration, frequency, and handling. We control via dummy variables for each dosage form that the focal manufacturing facility is capable of producing at the time of inspection. We also control for whether the drug products manufactured require a sterile environment, as the FDA views sterility as posing a higher potential for public health consequences should there be defects (FDA 2004). Finally, we control for the size of the manufacturing facility. On the one hand, large manufacturing facilities face a greater likelihood of inspection. On the other hand, large manufacturing facilities likely have superior organizational, managerial,

and technological processes in place, via scale and scope economies, that subsequently improve cGMP compliance. Table 1 provides greater detail on the construction of the control variables.

We use fixed effects to control for unmeasured variation that might result from differences in FDA district offices and investigators. There are 20 unique FDA district offices (including headquarters) located regionally throughout the United States. Hundreds of FDA investigators have inspected at least one manufacturing facility over the time period of our study. We confine our analysis to the most prolific FDA investigators in terms of cGMP inspections (those who have conducted at least 10 inspections). There are hundreds of manufacturing facilities that have been inspected at least once over the time period of our study. As with FDA investigators, we confine our fixed effects analysis to those facilities that have received the most inspections (those that have experienced at least five inspections).

3.4. Summary Statistics

Our unit of observation is the manufacturing facility inspection, defined according to whether and when the facility was inspected and, if so, the outcome of that inspection. The resulting data sample represents more than 10,000 unique cGMP inspections of more than 2,400 manufacturing facilities both domestically and abroad over the period 1990–2003.

Table 2 provides summary statistics for the dependent, independent, and control variables. All of the variables exhibit fairly substantial heterogeneity. The FDA inspects manufacturing facilities for cGMP compliance roughly every 500 days on average, but substantial variation in this measure exists. The predominant cGMP inspection outcome is VAI, although both NAI and OAI are well represented. Surveillance Inspection is the most frequent reason for inspection, while Compliance Inspection is relatively less frequent and Customer Complaint Inspection is relatively rare. A small percentage of the cGMP inspections in our sample take place in foreign manufacturing facilities. Most of the manufacturing facilities have a good reputation with the FDA, while a small percentage of the manufacturing facilities have a bad reputation with the FDA. An equal percentage of manufacturing facilities in our sample have a deteriorating reputation as have an improving reputation. Investigators have completed on average roughly a single training course (main or supplemental) and more than a dozen cGMP inspections prior to the focal cGMP inspection. All of the manufacturing-facility-specific control variables represent nonexclusive categories. For example, a pharmaceutical process inspected in a manufacturing facility might be for a prescription (versus over-the-counter) drug in a prompt-release profile and soft gel cap dosage form. Moreover, the manufacturing facility itself might have several different prescription drugs, release profiles, or dosage forms in operation in a given facility-year.

Table 3 provides correlation statistics for the dependent, independent, and

Table 2
Summary Statistics

Variable	Mean	SD	Min	Max
Dependent:				
Inspection Frequency	489.07	513.90	1.00	4,830.00
NAI	.38	.49	.00	1.00
VAI	.43	.49	.00	1.00
OAI	.19	.39	.00	1.00
Inspection decision:				
Days between Inspections	5.57	1.30	.69	8.48
Surveillance Inspection	.63	.48	.00	1.00
Compliance Inspection	.37	.48	.00	1.00
Customer Complaint Inspection	.00	.05	.00	1.00
Foreign Inspection	.13	.34	.00	1.00
Good Reputation	.66	.47	.00	1.00
Bad Reputation	.08	.27	.00	1.00
Improving Reputation	.13	.33	.00	1.00
Deteriorating Reputation	.13	.34	.00	1.00
Investigator:				
Cumulative Inspections	2.81	.98	.69	5.02
Core Courses	.58	.83	.00	4.00
Supplemental Courses	.38	.74	.00	5.00
Total Courses	.96	1.12	.00	6.00
Control:				
Prescription	.67	.47	.00	1.00
Prompt release	.20	.40	.00	1.00
Extended/delayed release	.07	.25	.00	1.00
Gel cap	.07	.26	.00	1.00
Soft gel cap	.01	.10	.00	1.00
Ointment	.07	.26	.00	1.00
Liquid	.16	.36	.00	1.00
Powder	.03	.16	.00	1.00
Gas	.00	.03	.00	1.00
Parenteral	.12	.33	.00	1.00
LV parenteral	.01	.10	.00	1.00
Aerosol	.01	.11	.00	1.00
Bulk	.16	.37	.00	1.00
Suppository	.01	.09	.00	1.00
Sterile	.04	.20	.00	1.00
Products	2.70	1.22	.69	5.16

control variables. A longer time period between successive cGMP inspections is positively associated with VAI inspection outcomes, Surveillance Inspection, Foreign Inspection, and Good Reputation and negatively correlated with OAI inspection outcomes, Compliance Inspection, Bad Reputation, and Deteriorating Reputation. Official Action Indicated inspection outcomes are positively correlated with Compliance Inspection, Bad Reputation, and Deteriorating Reputation and negatively correlated with Surveillance Inspection, Foreign Inspection, Good Reputation, and some of the investigator training variables.

Table 3
Correlation Statistics

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
1. Inspection Frequency	1.00																
2. NAI	−.02	1.00															
3. VAI	.05*	−.68*	1.00														
4. OAI	−.05*	−.38*	−.42*	1.00													
5. Days between Inspections	.80*	−.04*	.06*	−.02	1.00												
6. Surveillance Inspection	.16*	.11*	.02	−.17*	.12*	1.00											
7. Compliance Inspection	−.16*	−.11*	−.02	.17*	−.12*	−.99*	1.00										
8. Customer Complaint Inspection	−.02	.00	−.01	.00	−.02*	−.07*	−.04*	1.00									
9. Foreign Inspection	.21*	−.05*	.08*	−.05*	.19*	.03*	−.03*	−.02	1.00								
10. Good Reputation	.08*	.12*	.04*	−.20*	.03*	.23*	−.23*	.00	.00	1.00							
11. Bad Reputation	−.06*	−.09*	−.07*	.20*	−.03*	−.17*	.17*	−.01	−.03*	−.40*	1.00						
12. Improving Reputation	.03	−.03*	.03*	.01	.02*	−.03*	.03*	.01	.02	−.54*	−.11*	1.00					
13. Deteriorating Reputation	−.09*	−.07*	−.02*	.12*	−.05*	−.16*	.16*	−.01	.00	−.55*	−.11*	−.15*	1.00				
14. Cumulative Inspections	.10*	.02*	.00	−.03*	.13*	.01	−.01	−.03*	.18*	−.01	.00	.01	.00	1.00			
15. Core Courses	.15*	−.02*	.03*	−.01	.15*	−.01	.01	−.02*	.00	−.01	.02	.01	−.01	.28*	1.00		
16. Supplemental Courses	.02	−.01	.03*	−.03*	.04*	.00	.00	−.01	.06*	.01	.00	.00	−.02	.16*	.02*	1.00	
17. Total Courses	.12*	−.03*	.04*	−.02	.13*	.00	.01	−.02	.04*	.00	.01	.01	−.02	.31*	.75*	.67*	1.00

* Indicates pairwise significance at the .05 level.

3.5. Econometric Results

The tables in this section present the empirical results of the inspection frequency and inspection outcome analyses and provide several robustness tests for the inspection outcome analysis. All of the models presented easily reject likelihood-ratio null hypothesis tests for the inclusion of fixed effects and control and independent variables, at least at the .01 level. The models also adjust standard errors for robustness and within-manufacturing-facility clustering. Given the construction of some of the independent variables, we restrict the sample to those manufacturing facilities that received at least two inspections. This action modestly reduces the number of observations available. The analyses include manufacturing-facility-level covariates as controls, but the tables report only those variables germane to our analyses—namely, the FDA inspection decision variables and the FDA investigator training and experience variables.

3.5.1. Results for Inspection Hazard Rate

Table 4 presents the results for the inspection frequency (event history) analysis. Model 1 uses the exponential distribution model, while models 2 and 3 use the Gompertz and Cox proportional hazard models, respectively. Individual coefficients across these models are nearly identical in magnitude, sign, and statistical significance. The A models represent a baseline and include the manufacturing facility control variables and FDA district office (DO) fixed effects. The B models add FDA inspection decision variables for the reason for inspection (Compliance Inspection or Customer Complaint Inspection), the location of inspection (Foreign Inspection), and the manufacturing facility's reputation (Bad Reputation, Improving Reputation, and Deteriorating Reputation) to the A models. The C models add manufacturing facility fixed effects to the B models. We focus our discussion on the B and C results across each model.

Compliance Inspection increases the hazard of inspection ($p < .01$ in all models), indicating that the FDA shortens the time between cGMP inspections when manufacturing facilities establish new processes or modify existing processes. The results indicate that the hazard of inspection increases by an average of roughly 20 percent as a consequence of a compliance-driven inspection, in comparison to a surveillance-driven inspection.[13] Customer Complaint Inspection reduces the time between inspections ($p < .05$ in all models), while Foreign Inspection generally increases the time between inspections ($p < .01$ in all models). These results are largely unsurprising. The increased hazard of inspection attributable to customer complaints suggests that the FDA seeks to utilize information available from third parties (here, customers or consumers) as a

[13] We examine the probabilistic increase (or decrease) in the hazard of inspection (that is, the probability that an inspection will occur in time $t + 1$, given no inspection at time t). The increase (or decrease) in the hazard of inspection for a particular variable is derived by taking the exponential of that coefficient, $\exp(\beta_i)$, at a particular value and dividing it by the exponential of the coefficient at another (base) value.

Table 4
Inspection Frequency Results

	(1)			(2)			(3)		
	A	B	C	A	B	C	A	B	C
Constant	−6.98**	−6.99**	−6.96**	−6.90**	−6.94**	−6.99**			
	(.05)	(.06)	(.39)	(.05)	(.05)	(.40)			
γ				.00**	.00**	.00*			
				(.00)	(.00)	(.00)			
Compliance Inspection		.20**	.15**		.20**	.16**		.21**	.16**
		(.03)	(.03)		(.03)	(.03)		(.03)	(.03)
Customer Complaint Inspection		.49*	.62*		.48*	.66*		.34+	.50*
		(.21)	(.28)		(.21)	(.29)		(.19)	(.26)
Foreign Inspection		−.23**	.93*		−.26**	−.93*		−.22**	−1.31**
		(.04)	(.39)		(.04)	(.39)		(.04)	(.23)
Bad Reputation		.12*	.08		.13**	.07		.12*	.07
		(.05)	(.06)		(.05)	(.06)		(.05)	(.06)
Improving Reputation		−.01	.03		−.01	.02		−.04	.00
		(.03)	(.04)		(.03)	(.04)		(.03)	(.04)
Deteriorating Reputation		.24**	.17**		.25**	.16**		.23**	.14**
		(.03)	(.04)		(.03)	(.04)		(.03)	(.04)
N	7,858	7,858	6,033	7,858	7,858	6,033	7,858	7,858	6,033
Wald (χ^2)	1,927.8**	1,392.7**	2,764.1**	1,179.8**	1,609.7**	2,598.7**	1,723.7**	2,268.4**	2,613.1**
Log pseudo-likelihood	3,764.5	3,340.5	5,153.3	3,691.9	3,794.2	5,159.3	−51,363.6	−51,274.3	−35,381.5

Note. All models include control variables and Food and Drug Administration district office fixed effects; C models include manufacturing facility fixed effects.
+ $p < .10$.
* $p < .05$.
** $p < .01$.

vehicle to better manage its underendowment of information regarding inspection targets. The reduced hazard of inspection associated with foreign manufacturing facilities is likely a reflection of the significant additional costs incurred in conducting foreign inspections, in comparison to domestic inspections.

The results of the B models in Table 4 indicate that a manufacturing facility with a bad reputation ($p < .05$) or a deteriorating reputation ($p < .01$) faces a more frequent inspection pattern than does a manufacturing facility with a good reputation (the omitted category). These results suggest that the FDA relies on manufacturing facilities' reputation, using information secured from prior inspections to allocate inspection resources. But the estimation results also reveal a dynamic quality to the way the FDA uses the information secured from prior inspections for inspection decisions, which sheds light on the conduct of its day-to-day regulatory activities. Drawing on the estimated coefficients, we find that manufacturing facilities with bad reputations face a hazard of inspection that is 13 percent greater than facilities with good reputations, whereas manufacturing facilities with deteriorating reputations face a hazard of inspection that is 27 percent greater than facilities with good reputations. Quite simply, poor previous cGMP performance by manufacturing facilities invites increased regulatory scrutiny on the part of the FDA. The estimation results thus reveal not only the importance of regulators' propensity to draw on information from prior inspections, but also the costly regulatory consequences that manufacturing facilities bear from lapses in cGMP compliance.

The C models add manufacturing facility fixed effects to the B models. We select those manufacturing facilities that have received at least five inspections,[14] which modestly reduces the sample size in comparison to previous models. Compliance Inspection and Customer Complaint Inspection maintain their positive and statistically significant effects on inspection frequency, while Foreign Inspection somewhat surprisingly remains statistically significant. Deteriorating Reputation maintains its positive and statistically significant effect on inspection frequency, while Bad Reputation loses its statistical significance.

3.5.2. Inspection Outcomes

Table 5 presents the results of the inspection outcome analysis, using OAI (complete noncompliance) as the dependent variable. Model 1 includes FDA DO fixed effects and the manufacturing facility control variables. Model 2 adds the FDA inspection decision variables to model 1, while model 3 adds the FDA

[14] Summary statistics confirm that manufacturing facilities with more than five inspections are essentially identical to those with five or fewer inspections along the following dimensions: facility-specific factors (for example, dosage forms or release profiles), inspection outcomes, reasons for inspection, facility reputation, and investigator-specific factors. Some statistical differences do exist between these sets of facilities along the following dimensions: prescription products (larger for facilities with more than five inspections), number of drug products manufactured (larger for more than five inspections), days between inspections (smaller for more than five inspections), and foreign inspections (smaller for more than five inspections).

Table 5
Results of Inspection Outcome Analysis

	(1)	(2)	(3)	(4)	(5)	(6)
Constant	−.87**	−1.31**	−.68**	−1.17**	−1.09	−.21
	(.08)	(.12)	(.10)	(.13)	(.71)	(1.14)
Days between Inspections		.02*		.03*	.06**	.09**
		(.01)		(.01)	(.02)	(.02)
Compliance Inspection		.32**		.33**	.31**	.29**
		(.04)		(.04)	(.04)	(.05)
Customer Complaint Inspection		.14		.10	.17	−.06
		(.28)		(.28)	(.28)	(.38)
Foreign Inspection		−.04		−.02	−.11	−.46
		(.06)		(.06)	(.07)	(1.34)
Bad Reputation		.84**		.85**	.78**	.17*
		(.06)		(.06)	(.06)	(.08)
Improving Reputation		.20**		.20**	.18**	−.21**
		(.05)		(.05)	(.06)	(.07)
Deteriorating Reputation		.48**		.48**	.47**	.05
		(.05)		(.05)	(.06)	(.06)
Cumulative Inspections			−.05*	−.05**	−.07*	−.09**
			(.02)	(.02)	(.03)	(.03)
Total Courses			−.07+	−.08*	−.10+	−.09+
			(.04)	(.04)	(.06)	(.05)
N	7,858	7,858	7,858	7,858	6,480	4,885
Wald (χ^2)	153.3**	635.8**	161.5**	664.7**	742.7**	768.9**
Pseudo-R^2	.026	.086	.028	.086	.147	.141
Log likelihood	−3,765.7	−3,543.5	−3,756.6	−3,533.7	−2,811.6	−2,351.6

Note. The dependent variable is Official Action Indicated. All models include control variables and Food and Drug Administration district office fixed effects; model 5 includes investigator fixed effects, and model 6 includes manufacturing facility fixed effects. Probit estimation is used in all models.

+ $p < .10$.

* $p < .05$.

** $p < .01$.

investigator experience and training variables to model 1.[15] Model 4 adds both FDA inspection decision variables and FDA investigator experience and training variables to model 1. Models 5 and 6 test the robustness of these specifications by adding, respectively, investigator fixed effects and manufacturing facility fixed effects to model 4.

The estimation results in Table 5 are very encouraging. Days between Inspections increases the likelihood of complete noncompliance ($p < .05$) in all models. Two possible (and not necessarily competing) reasons explain this result. First, manufacturing facilities may be more likely to let their manufacturing processes atrophy into noncompliance with the passage of time.[16] Second, investigators who are aware of a longer time between inspections may more thoroughly scrutinize the focal manufacturing facility during cGMP inspection. Regardless of whether the first, second, or some combination of these explanations drives this result, it suggests that the information signal provided by the number of days between successive cGMP inspections is an important predictor of regulatory outcomes.

The results in Table 5 also indicate that a manufacturing facility undergoing a compliance inspection is more likely to be found cGMP noncompliant ($p < .01$ in all models) than is a facility facing a regular and periodic surveillance inspection. Given that any manufacturing process change creates cGMP compliance uncertainty, this result is perhaps not surprising.[17] But this result does nevertheless suggest that regulators seek to close the information asymmetry gap by drawing on the information provided by manufacturing facilities when those facilities establish new manufacturing processes or change their existing processes. Interestingly, while Customer Complaint Inspection significantly shortens inspection frequency, this variable does not have a statistically significant effect

[15] A potential confound arises if inspectors are linked in a systematic fashion to particular manufacturing facilities. With limited exceptions, the FDA randomizes inspectors to the manufacturing facilities that they inspect. In this regard, it is also important to note that the FDA administration, rather than the inspectors themselves, makes the decision of which facilities will be inspected, when, and by whom. Consequently, we consider that the choice of inspectors is, from an econometric perspective, exogenous and not the source of any endogeneity confounds. In certain situations (for example, follow-up inspections), it is sensible for the same FDA investigator to inspect the same manufacturing facility twice, especially if the facility was previously found noncompliant. Thus, some regularity of inspections by individual regulators at particular facilities is expected. To explore this, we examined empirically the repetition of inspections by individual regulators at specific manufacturing facilities. The results indicate that the same regulator visits the same manufacturing facility for two consecutive inspections only 14.5 percent of the time, and this rate falls to 4.4 percent and 1.8 percent, respectively, for three and four consecutive inspections. Manufacturing facilities that receive more inspections are also visited by more and different FDA investigators. The pairwise correlation coefficient between the number of manufacturing facility inspections and the number of distinct FDA investigators is .90.

[16] While the passage of time allows for degradation in the likelihood of compliance, ceteris paribus, a second and separate effect (as identified empirically in Table 4) is as follows. Contingent on the outcome of a given inspection of a manufacturing facility, the greater the compliance of the facility, the longer the time before the FDA reinspects it.

[17] If compliance inspections that identify compliance failures are met with corrective actions by manufacturing facilities, then subsequent compliance rates identified through standard surveillance inspections may be similar to (or even better than) those of the population of other inspections.

on cGMP compliance. This result plausibly suggests that while the FDA uses customer complaints as an information signal for targeting inspections, the information content of that signal is relatively weak. The results in Table 5 also reveal no robust statistically significant effect from Foreign Inspection, which indicates that foreign facilities are in cGMP compliance with roughly the same probability as their domestic counterparts. We return to this result in Section 3.5.3.

The results in Table 5 provide strong support for the importance of the reputation variables. A manufacturing facility with a bad reputation is significantly more likely to be found in complete noncompliance in the current cGMP inspection ($p < .05$ in all models) than is a manufacturing facility with a good reputation. A manufacturing facility with either an improving reputation or a deteriorating reputation is similarly more likely to be found completely noncompliant in the current cGMP inspection ($p < .01$ in most models) than is a facility with a good reputation. These results suggest that the FDA relies on the information available from prior regulatory lapses in its current inspections. The economic interpretation of these results is also interesting. Using the manufacturing facility reputation coefficients in model 4, we find that the likelihood that a manufacturing facility with a bad reputation, a deteriorating reputation, or an improving reputation will be found in complete noncompliance increases—relative to a manufacturing facility with a good reputation—by roughly 134, 62, and 22 percent, respectively.

Table 5 also indicates statistically significant effects associated with inspectors' experience and training. In particular, Cumulative Inspections reduces the likelihood that a manufacturing facility is found to be out of cGMP compliance ($p < .05$ in all models). This result suggests that the information accumulated over time by individual FDA investigators significantly influences the likelihood that they will find manufacturing facilities to be out of compliance. Investigators who have received more training—measured via Total Courses—are similarly less likely to find a manufacturing facility cGMP noncompliant (although the results are not statistically significant in all estimations). We return to these FDA investigator findings in Section 3.5.3.

Models 5 and 6 test the robustness of these main results by adding investigator and manufacturing facility fixed effects, respectively. We select those investigators who have conducted at least 10 cGMP inspections and those manufacturing facilities that have received at least five inspections, respectively. The results of these models are broadly consistent with the earlier specifications in terms of magnitude, sign, and statistical significance.

3.5.3. Robustness Results

Table 6 presents several robustness tests of the inspection outcome analysis. The models in Table 6 are in comparison to model 4 of Table 5, which is repeated as model 1 in Table 6 to ease exposition. Model 2 examines via the inclusion

of squared terms whether investigator experience or investigator training have any nonlinear effects on inspection outcomes. The results for model 2 indeed indicate significant nonlinear effects from both investigator experience and investigator training. With nonlinear terms added, the effect of Cumulative Inspections is negative and significant, while its squared term is positive and significant. This result suggests that relatively inexperienced and relatively experienced investigators are more likely to find manufacturing facilities cGMP noncompliant. Ceteris paribus, we find that the likelihood of noncompliance outcomes peaks for investigators with roughly 10 inspections. This U-shaped pattern holds for investigator training as well. In particular, FDA investigators with relatively limited or relatively significant training in terms of the number of core and supplemental drug courses taken are less likely to find manufacturing facilities to be noncompliant, while more modestly trained investigators are more likely.

Model 3 examines whether greater specificity in the types of courses taken by FDA investigators influences the cGMP inspection outcomes of manufacturing facilities. Recall that our data track the number of core courses (those on general pharmaceutical manufacturing topics) and supplemental courses (those on specialty topics). The results indicate that supplemental courses provide some benefit or additional information to FDA investigators in their determinations of cGMP noncompliance, while core courses do not appear to provide any such benefit or information.

Models 4–6 of Table 6 use VAI as the dependent variable and reinforce our earlier finding that Days between Inspections is a significant determinant of cGMP inspection outcomes ($p < .05$ in all models). However, a manufacturing facility undergoing a compliance inspection is not more likely to be found mildly noncompliant than a facility undergoing a general surveillance inspection. Interestingly, foreign manufacturing facilities are significantly more likely ($p < .01$ in all models) to be found mildly noncompliant than domestic manufacturing facilities across all models.

The VAI results provide some nuanced insights into the relation between inspection outcomes and manufacturing facilities' reputations. Recall from Table 5 that a manufacturing facility with a bad reputation is more likely to be found in complete noncompliance in the current cGMP inspection. In contrast, a manufacturing facility with a bad reputation is less likely to be found in mild noncompliance in the current cGMP inspection ($p < .01$ in all models) than is a facility with a good reputation. In short, manufacturing facilities with bad reputations are more likely to be found completely noncompliant than mildly noncompliant. Similarly, while Deteriorating Reputation increases the likelihood of a manufacturing facility's being in complete noncompliance, it reduces the likelihood of its being in mild noncompliance ($p < .05$ in all models).

The effects of the FDA investigator experience and training variables on VAI inspection outcomes are also interesting. Model 4 indicates that FDA investigators with more experience are less likely to find manufacturing facilities mildly non-

compliant ($p < .05$), while those with more training are more likely to do so ($p < .05$). The former result is in contrast to the results using OAI as the dependent variable in Table 5. Model 5 in Table 6 indicates no statistically significant nonlinear effects from FDA investigators' cumulative inspection experience or total courses taken. Model 6 indicates that Core Courses ($p < .10$) and Supplemental Courses ($p < .05$) increase the probability that a manufacturing facility receives a VAI inspection outcome—a result in contrast to the results in model 3 of Table 6, where OAI is the dependent variable.

We also examined but do not report three other robustness tests. In the first test, we replaced probit estimation with multinomial logit estimation, using NAI as the base category. Recognizing that assumptions of independence and specific cardinal ordering among alternative outcomes can be questioned, we found that the results not surprisingly followed those of Table 6. In the second test, we replaced probit estimation with ordered probit estimation. This estimation approach presumes that a natural noncompliance ordering—increasing in severity from NAI to VAI to OAI—exists among inspection outcomes. The results were also strongly similar to our earlier probit models. In particular, all of the FDA inspection decision variables and FDA investigator experience and training variables maintained statistical significance. In the third test, we altered our reputation variables using a one-period lag structure rather than a two-period lag structure.[18] In this classification, we specified manufacturing facilities with bad reputations as those that received an OAI in the most recent inspection and manufacturing facilities with good reputations as those that received an NAI in the most recent inspection. The base case reputation, which is neither improving nor deteriorating, is associated with a VAI outcome. The results indicate that facilities with bad reputations are more likely to be inspected ($p < .01$ in all models), while facilities with good reputations are less likely to be inspected ($p < .05$ in all models).

3.6. Discussion

Our econometric analyses identify several important empirical regularities. First, we find that regulators do not passively accept the information asymmetry gap that they confront. Both the frequency and stringency of inspections are influenced by systematic efforts on the part of regulators to take advantage of alternative means to narrow the gap. Our examination of the regulatory decision to inspect manufacturing facilities for cGMP compliance indicates that regulators draw on a number of information signals in lieu of direct observations to modify their subsequent inspection behavior. For instance, the FDA systematically alters its inspection frequency on the basis of the source of the inspection prompt.

[18] Note that anything beyond a two-period lag structure suffers from interpretation difficulties regarding reputation. For instance, a three-period lag structure results in 27 unique inspection outcome permutations. Ranking these permutations in terms of good, increasing, decreasing, and bad reputations is a subjective exercise at best.

Table 6

Robustness Results for Inspection Outcomes

	OAI			VAI		
	(1)	(2)	(3)	(4)	(5)	(6)
Constant	−1.17**	−.73**	−1.26**	−.10	−.28	−.05
	(.13)	(.22)	(.14)	(.12)	(.19)	(.12)
Days between Inspections	.03*	.03*	.04**	.03*	.04**	.03*
	(.01)	(.02)	(.02)	(.01)	(.01)	(.01)
Compliance Inspection	.33**	.33**	.34**	.00	.00	.01
	(.04)	(.04)	(.04)	(.03)	(.03)	(.03)
Customer Complaint Inspection	.10	.09	.09	−.14	−.28	−.44
	(.28)	(.31)	(.27)	(.29)	(.29)	(.32)
Foreign Inspection	−.02	−.09	−.05	.27**	.22**	.24**
	(.06)	(.06)	(.06)	(.05)	(.05)	(.05)
Bad Reputation	.85**	.87**	.87**	−.29**	−.25**	−.26**
	(.06)	(.06)	(.06)	(.06)	(.06)	(.06)
Improving Reputation	.20**	.20**	.21**	.00	.02	.01
	(.05)	(.05)	(.05)	(.05)	(.05)	(.05)
Deteriorating Reputation	.48**	.49**	.52**	−.10*	−.14**	−.12**
	(.05)	(.05)	(.05)	(.05)	(.05)	(.05)
Cumulative Inspections	−.05**	−1.78**	−.05*	−.04*	.65	−.03+
	(.02)	(.57)	(.02)	(.02)	(.48)	(.02)
Cumulative Inspections^2		.80**			−.32	
		(.26)			(.22)	
Total Courses	−.08*	−.10*		.06**	.02	
	(.04)	(.04)		(.01)	(.03)	
Total Courses^2		.02*			.01	
		(.01)			(.01)	
Core Courses			−.04			.03+
			(.04)			(.02)
Supplemental Courses			−.11*			.06*
			(.05)			(.02)
Wald (χ^2)	664.7**	652.4**	711.8**	246.0**	248.6**	228.3**
Pseudo-R^2	.086	.087	.083	.025	.027	.024
Log likelihood	−3,533.7	−3,490.4	−3,459.7	−5,233.0	−5,227.8	−5,243.3

Note. All models include control variables and Food and Drug Administration district office fixed effects. Probit estimation is used in all models. OAI = official action indicated; NAI = no action indicated. N = 7,858.

+ $p < .10$.

* $p < .05$.

** $p < .01$.

While regulators may seem to simply go about their business as a result of statutory requirements to inspect manufacturing facilities, our results indicate that they also use cues from both the manufacturing facilities (for example, notice of changes in processes) and consumers and customers (for example, complaints) to alter their inspection behaviors. Regulators also seek to overcome the information asymmetry gap by drawing on other available information and data sources. In particular, regulators draw on information secured through previous inspections to form heuristic reputations for manufacturing facilities that, in turn, are used to guide and influence regulatory decisions. A manufacturing facility with a previously earned good reputation is met with more of a regulatory hands-off approach, while a facility with a previously earned bad reputation is scrutinized more thoroughly. This result is especially telling, as it indicates that in the face of regulators' inability to detect certain relevant features of a manufacturing facility (for example, whether any operational, technical, or managerial practices are lacking or the physical infrastructure imposes undue risks), regulators find ways to narrow, even if imperfectly, the information asymmetry gap.

Second, the time span and breadth of the panel data we employ permit us to identify the importance of FDA regulators' experience and training as determinants of regulatory outcomes. As FDA investigators move down the learning curve associated with cGMP inspections, they accumulate information. Cumulative inspection experience decreases the probability that the FDA investigator will find a manufacturing facility in complete noncompliance. To place an economic interpretation on this finding, we use the results in model 4 in Table 5 to estimate the difference in the probability of an OAI outcome for investigators with 1 standard deviation more inspection experience (roughly 22 inspections) than the mean level of inspection experience (roughly 24 inspections). Investigators with 1 standard deviation more inspection experience are roughly 2 percent less likely to find manufacturing facilities cGMP noncompliant than are investigators with the mean level of inspection experience. Regulator experience is thus seen to have discernible effects on regulatory outcomes.

Finally, we find that regulatory outcomes vary sharply across individual regulators. Even after controlling for a wide array of manufacturing-facility-specific variables and FDA inspection decision variables, we find that the likelihood of a manufacturing facility's being found cGMP noncompliant varies markedly by the individual FDA investigator. In short, investigator-specific effects significantly affect regulatory outcomes. For instance, 18 percent of investigators identified in our analysis have statistically significant effects on the probability of an OAI outcome compared to the mean investigator. To get an economic sense of the effect that individual FDA investigators have, we use model 5 in Table 5 to estimate the increase in the probability of an OAI outcome by investigator. Figure 1 presents a histogram of the distribution of these probabilities. The investigator with the largest positive (negative) effect compared to the mean investigator increases (decreases) the probability of an OAI outcome by roughly 25 (18)

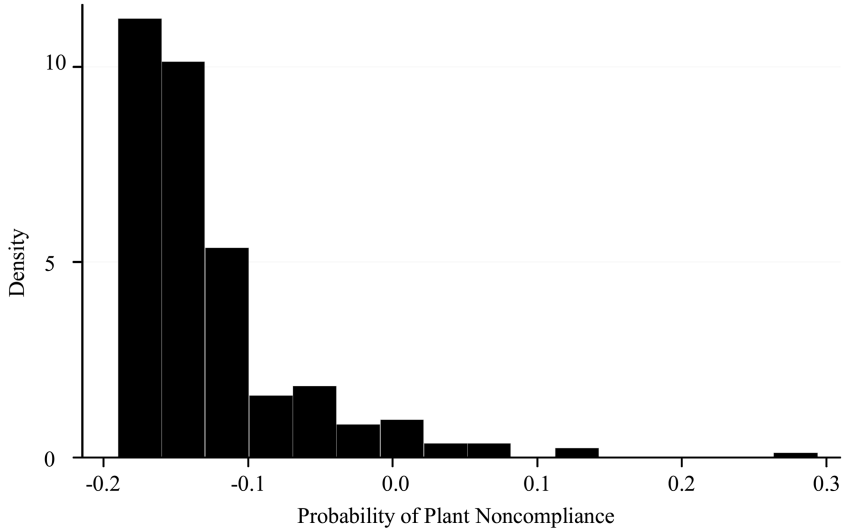

Figure 1. Probability that Food and Drug Administration investigators find noncompliance with current good manufacturing practices.

percent. This analysis thus establishes an empirical regularity even after accounting for the accumulation of human capital through training and experience. In short, regulators (here, FDA investigators) are markedly heterogeneous.[19]

4. Conclusion

Over the past 2 decades, increasing theoretical sophistication has been brought to modeling the relationship between regulators and the firms they regulate. A main vehicle for these advances has been the principal-agent model, which most often assumes the presence of an exogenous information asymmetry between the principal (the regulator) and the agents (the firms it regulates). This focus has in turn led to a design of optimal regulatory mechanisms under the assumption of these given information asymmetries. Our paper seeks to shed light on a heretofore underexplored aspect of the information asymmetry gap: the considerable effort engaged in by real-world regulators on a day-to-day basis to overcome information asymmetries. To do so, we investigate the extent to which

[19] While our data include granular information on each inspection and detailed information on investigators' experience and training, data on individual compensation and reward mechanisms for individual inspectors were unattainable. On the basis of conversations with FDA management, our understanding is that inspectors' compensation has no direct or indirect tie to inspection outcomes. We were also unable to obtain other information on individual investigators, such age, race, gender, and the like.

regulators use previously secured information to guide their regulatory (inspection) decisions. In addition, we explore the role that regulators' experience and training (along with a host of other controls) have in affecting regulatory outcomes.

Our analysis incorporates a rich panel data set of over 10,000 individual regulatory inspections of over 2,400 manufacturing facilities around the world over a 14-year period. Our results provide considerable evidence that regulators are actively aware of information asymmetries and engage in a variety of activities designed to mitigate the information asymmetries they would otherwise face. Among the most prominent behaviors, regulators use information secured from prior interactions with manufacturing facilities and engage in training individual investigators to better equip them to overcome such asymmetries. Our results also reveal marked heterogeneity among individual regulators, suggesting that future theoretical efforts may benefit from accounting for this empirical regularity. More generally, our results suggest that future models (both theoretical and empirical) of the interaction of the regulator and the regulated firm are likely to benefit from incorporating regulators' efforts at overcoming information asymmetries. Our analysis also points toward an important reality of regulator heterogeneity that is in need of greater exploration.

References

Armstrong, Mark, and David E. M. Sappington. 2007. Recent Developments in the Theory of Regulation. Pp. 1557–1700 in vol. 3 of *Handbook of Industrial Organization,* edited by Mark Armstrong and Robert Porter. Amsterdam: Elsevier.

Averch, Harvey, and Leland L. Johnson. 1962. Behavior of the Firm under Regulatory Constraint. *American Economic Review* 52:1052–69.

Baron, David P. 1989. Design of Regulatory Mechanisms and Institutions. Pp. 1347–1447 in vol. 2 of *Handbook of Industrial Organization,* edited by Richard Schmalensee and Robert Willig. North Holland: Elsevier.

Baron, David P., and David Besanko. 1984. Regulation, Asymmetric Information and Auditing. *RAND Journal of Economics* 15:447–70.

———. 1987. Monitoring, Moral Hazard, Asymmetric Information, and Risk Sharing in Procurement Contracting. *RAND Journal of Economics* 18:509–32.

Blank, Larry, and John W. Mayo. 2009. Endogenous Regulatory Constraints and the Emergence of Hybrid Regulation. *Review of Industrial Organization* 35:233–55.

Feinstein, Jonathan S. 1989. The Safety Regulation of U.S. Nuclear Power Plants: Violations, Inspections, and Abnormal Occurrences. *Journal of Political Economy* 97:115–54.

———. 1990. Detection Controlled Estimation. *Journal of Law and Economics* 33:233–76.

FDA (Food and Drug Administration). 2004. Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—a Pilot Risk Ranking Model. Unpublished report. Department of Health and Human Services, U.S. Food and Drug Administration, Washington, D.C.

Fremeth, Adam, and Guy L. F. Holburn. Forthcoming. Information Asymmetries and Regulatory Decision Costs: An Analysis of Electric Utility Changes, 1980–2000. *Journal*

of Law, Economics, and Organization 28. Published electronically February 2, 2010. doi: 10.1093/jleo/ewp042.

Khalil, Fahad. 1997. Auditing without Commitment. *RAND Journal of Economics* 28:629–40.

King, Andrew, and Michael Lennox. 2000. Industry Self-Regulation without Sanctions: The Chemical Industry's Responsible Care Program. *Academy of Management Journal* 43:105–16.

Laffont, Jean-Jacques, and D. Martimort. 2002. *The Theory of Incentives: The Principal-Agent Model.* Princeton, N.J.: Princeton University Press.

Mathieu, Mark. 2000. *New Drug Development: A Regulatory Overview.* Waltham, Mass.: Parexel International.

Maxwell, John W., Thomas P. Lyon, and Steven C. Hackett. 2000. Self-Regulation and Social Welfare: The Political Economy of Corporate Environmentalism. *Journal of Law and Economics* 43:583–618.

Weil, David. 1996. If OSHA Is So Bad, Why Is Compliance So Good? *RAND Journal of Economics* 27:618–40.