

**REGULATOR HETEROGENEITY AND ENDOGENOUS EFFORTS TO
CLOSE THE INFORMATION ASYMMETRY GAP:
EVIDENCE FROM FDA REGULATION**

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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 dataset of regulatory inspections conducted by the U.S. Food and Drug Administration 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, if not altogether inconsistent with, the key practical realities of regulation by the FDA. Our analysis uncovers several dimensions along which regulators actively 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 by which regulated entities must, under threat of penalty, comply. Consequently, early economic models of regulation assumed that regulatory rules were sufficiently well-specified and binding so that neither regulators nor the firms they regulate had discretion in enforcing or adhering to these regulations. In the past two decades, however, economists 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.² Central to these models has been the assumption that regulators are under-endowed with information regarding the operating technology (i.e., costs or quality) of the regulated firm. This, in turn, has 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, assuming the presence of information asymmetry.³

While the optimal regulatory design literature has significantly advanced our understanding of economic regulation, it is less than satisfying on at least three grounds. First, although the research on optimal regulatory design mechanisms has generated considerable theoretical discussion, the actual implementation of these schemes is rare.⁴ As a practical matter, this result may spring from the significant (i.e., costly) changes to existing regulatory mechanisms that would be necessary to implement these “optimal” designs. Thus, despite

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

² For a comprehensive survey, see Laffont and Martimort (2002).

³ See Baron (1989) and Armstrong and Sappington (2007) for reviews.

⁴ Even the most notable shift of regulatory design instruments—from rate-of-return regulation to price-cap regulation within traditional public utility industries—is far from complete (Blank and Mayo, forthcoming). 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.

providing aspirant 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.⁵ 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. In this sense, the “exogenous” and “immutable” information asymmetry assumption is not congruent with the practical efforts by regulators that are made to overcome these asymmetries. Thus, while regulators expend considerable efforts in attempts to manage and reduce information asymmetries, the substantial thrust of the modeling attention to this point has been aimed at regulatory re-design 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. Regulatory agencies such as the Occupational, Safety and Health Administration (OSHA), the Nuclear Regulatory Commission (NRC) and the Food and Drug Administration (FDA), among others, are comprised of hundreds of regulatory “foot soldiers.” These armies of regulators are the individuals who visit firms and manufacturing facilities, implement complex regulations, determine and report violations, and incur 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 arises. If regulators are not homogenous and are 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 modern emphasis on the design of “optimal” regulatory mechanisms in the face of exogenous information asymmetries gives way to concerns about human capital development and

⁵ See Baron and Besanko (1984), Baron and Besanko (1987) and Khalil (1997) for notable exceptions.

management and organizational incentives and structures, as these factors become important features of the regulatory landscape.⁶

To probe the dimensions of these under-explored features of regulation, we focus on regulators in the context of the Food and Drug Administration (FDA). We chose the FDA because it has a substantial economic impact in the U.S. healthcare system and offers structural features that are similar to several other federal agencies. Like OSHA, the NRC and many other state and federal regulatory agencies, the FDA is comprised of hundreds of regulatory foot soldiers called “investigators.” Also, we have unprecedented access to data within a division of the agency—the Center for Drug Evaluation Research (CDER)—in charge of oversight and regulation of pharmaceutical drug products.⁷ Our sample represents a comprehensive 14-year panel data set between 1990 and 2003 of every inspection undertaken by more than 700 investigators at more than 2,400 pharmaceutical manufacturing facilities located 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 manufacturing facility. Second, the assumption of a single, monolithic principal (the regulator) is rather obviously violated in the context of the FDA. Whether 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 (i.e., uniform) in their behaviors. Accordingly, we explore the extent to which the army of regulators’ decisions are rational and uniform. The natural counter-hypothesis is that these foot soldiers enjoy only limited human capital, are boundedly rational, and display significant heterogeneity in their regulatory decisionmaking. In short, we seek to understand what possibilities exist in practice, and how

⁶ See Fremeth and Holburn (2012) for an examination of the effects of regulator experience, management and organization on reducing information asymmetries, and thereby, reducing regulator decision costs and facilitating policy-making.

⁷ Two of the authors are special government employees (SGEs) of the FDA, and in that capacity have been able to secure both extraordinarily granular and extensive data on the inner-workings of this agency.

effective these possibilities might be, 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 manufacturing of pharmaceutical drug products. The first decision 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 by past inspections and compliance to manage decisions of whether and when to conduct inspections. The second decision is whether, upon inspection, a manufacturing facility is identified as in compliance or not. This analysis again indicates that regulators draw significant information from prior performance to establish heuristic impressions of manufacturing facilities’ propensity for compliance. The reputations of the facilities being inspected, which stem from the information provided to regulators from past inspections, are shown to significantly alter regulatory outcomes.

Our analysis of regulatory outcomes also reveals a significant amount of regulator heterogeneity, with significant differences across FDA investigators in the propensity to find manufacturing facilities in violation of regulatory standards.⁸ We test for and find that investigator training and experience are critical determinants in generating regulatory heterogeneity. Nonetheless, even after accounting for variations in both investigator- and inspection-specific characteristics, as well as a variety of manufacturing facility-specific characteristics, we find pronounced evidence of regulator heterogeneity. *Ceteris paribus*, some investigators are forty percent more likely than the median investigator to impose sanctions on manufacturing facilities, while other investigators are twenty 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 re-designs to overcome the information asymmetry problems, we find tangible evidence on the part of regulators to mitigate this gap *within a given regulatory design*. Additionally, we find substantial variation in

⁸ For earlier empirical evidence of such regulator heterogeneity, see Feinstein (1989, 1990).

regulatory outcomes by investigator. Indeed, we find strong evidence of a clear and consistent empirical regularity: regulator heterogeneity is a tangible and significant empirical phenomenon that needs to be considered in the modeling and design of regulatory mechanisms.

Finally, our study investigates and identifies several sources of regulator heterogeneity. Regulatory outcomes are found to depend on the amount and type of training investigators receive and the frequency with which investigators participate in inspections, as well as unobserved investigator-specific factors. These findings provide strong evidence that regulatory outcomes can and do depend on the level of accumulated idiosyncratic investigator knowledge. We therefore confirm the oft-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 human capital heterogeneity 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 total or consumer surplus maximizing regulators.⁹ Over time, these models have given way to more sophisticated perspectives that allow regulated firms to possess knowledge of their production processes (e.g., cost or quality) to which regulators are not, without expenditure of resources, privy. Incorporating such asymmetric information into 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, fully aware that they are under-endowed with information, seek to design regulatory mechanisms to elicit (total or consumer) surplus maximizing behavior by regulated firms. 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.¹⁰

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

⁹ See, e.g., Averch and Johnson (1962).

violations is complete and regulators are unbounded on the extent of fines they may impose, then any initial information asymmetries enjoyed by firms can be overcome and regulatory non-compliance ended. In reality, inspections are costly, detection is not perfect and fines are bounded. Regulators thus face the challenge of overcoming their information asymmetries by deciding whether or not to inspect a given facility and how much to invest in detection efforts. It is these issues that will be the focus of our empirical model of FDA regulation.

The FDA is an agency of the U.S. Department of Health and Human Services (HHS) 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 food, medical, and cosmetic products.

The FDA is organized into six centers with separate responsibilities related to health and safety depending upon the product (i.e., food, drugs, medical devices) or end-user (i.e., human or animal).¹¹ 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 responsibility of the Center of Drug Evaluation Research (CDER). This division of the FDA seeks to ensure that medicinal drug products used for the treatment and prevention of disease are proven safe and effective before they are used by patients. Among its many duties, CDER regulates the introduction of new drug products, and the manufacture and distribution of approved drug products. Our focus is on the regulation of drug product manufacturing, as opposed to the review and approval of new drug molecules (i.e., drug development).

FDA is required by the Federal Food, Drug and Cosmetic Act of 1938 to inspect all registered manufacturing facilities that sell drug products within the United States, regardless of their 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 (i.e., finished dosage forms) and drug components (i.e., bulk and active pharmaceutical ingredients)

¹⁰ For a comprehensive survey, see Armstrong and Sappington (2007).

¹¹ 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 (CBER); (4) the Center for Veterinary

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).

Since establishing cGMP requirements in 1962, the FDA has taken a “general regulatory approach,” whereby only broad guidelines are provided to pharmaceutical firms related to cGMP compliance. Supplementary information, typically referred to as “guidances,” provide additional specificity only when necessary and usually around requirements related to manufacturing, quality control and documentation, or updates for process and methods validation. The FDA targets 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 manufacturing process step must be controlled to maximize the likelihood that finished drug products are safe and efficacious (Mathieu, 2000). cGMP regulations seek to ensure the quality of drugs by setting minimum standards for all manufacturing facilities in ten separate areas (Mathieu, 2000),¹² which apply to both approved drug products and experimental drug products operating under New Drug Application (NDA) status.

FDA implements the enforcement program related to manufacturing facility cGMP compliance. The Office of Regulatory Affairs 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 ORA and 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. FDA investigators are generally given wide latitude in conducting cGMP inspections around these ten areas.

After a cGMP inspection, manufacturing facilities are notified as to any violations. Formal inspection outcomes determine whether the manufacturing facility is in cGMP compliance (i.e., no violations) or out of cGMP compliance (i.e., in violation)—the latter requiring some response on the part of the manufacturing facility. Minor cGMP violations

Medicine (CVM); (5) the Center for Devices and Radiological Health (CDRH); and, (6) the National Center for Toxicological Research.

¹² 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.

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, FDA can and does escalate the severity of penalties, including but not limited to legal sanctions (i.e., fines, product seizures, injunctions and prosecutions), controlled distribution and/or limited marketing. FDA will propose such regulatory actions to the U.S. Justice Department and file cases with the U.S. District Court, 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 shirking of sound manufacturing practices. The extent of any such rents are determined by whether, and the extent to which, regulators undertake efforts to overcome information asymmetry gaps. Accordingly, we turn to two complementary empirical examinations that examine the efforts the FDA takes 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 FDA regulator—including levels of training and experience—affect regulatory outcomes, after controlling for other factors related to the manufacturing facility and the FDA inspection decision.

3.1.1 Risk of Inspection Analysis

Given the associated costs, we expect pharmaceutical manufacturing facilities to differ with respect to compliance related cGMP regulations. Indeed, over our 14 years of data only 18 percent of manufacturing facilities inspected are found to be in compliance over any two-year window, while the remaining 82 percent of manufacturing facilities have at least one (either minor or major) cGMP violation over any two-year window.

Knowing that some manufacturing facilities are likely to be compliant and others not, but with limited *ex ante* knowledge of which facilities fall into which category, the FDA faces a “first-tier” information asymmetry gap—namely, determining which facilities to inspect and

when. While the agency may be seen to nominally accomplish its goal of promoting cGMP practices through a system of random inspections, it is also likely that in making inspection selection decisions the FDA draws inferences from past experiences with the manufacturing facilities that it inspects. To investigate this possibility, we utilize 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 i at time t as:

$$r_i(t) = \lim_{t' \rightarrow t} \frac{\Pr(t \leq t' | T \geq t')}{t' - t}$$

We estimate models that specify the transition (or hazard rate) as a function of time t and a vector of covariates Z that represents our independent variables. This estimation approach takes the general form $r_i(t) = f(t, Z_{it})$. We employ three separate hazard models in our empirical approach—exponential, Gompertz and Cox Proportional—in order to explore to what extent assumptions about the hazard rate function affects our estimation results. The exponential model can be parameterized as either a proportional hazards or 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 the 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 individual FDA investigator characteristics (i.e., their levels of training and experience) influence the determination of cGMP compliance. Accordingly, we model the relationship between individual investigator characteristics and the likelihood of noncompliant cGMP outcomes. We anticipate that the unobserved probability of manufacturing facility being found noncompliant with respect to cGMP practices (C_{ijt}^*) depends upon a vector of variables related to the levels of

experience and training of the individual investigator (I_{ijt}) as well as a vector of other independent and control variables (X_{ijt}):

$$C_{ijt}^* = \beta_0 + \sum \beta I_{ijt} + \sum \gamma X_{ijt} + \mu_{ijt}$$

where β_0 is a constant term, β and γ are parameter vectors, and μ_{ijt} is a random error term.¹³ Because we do not observe this probability directly, we necessarily draw upon the tangible outcome of the inspection process. The outcome of any given inspection i of manufacturing facility j at time t (C_{ijt}) results in the facility being found in compliance or in violation of cGMP regulations. The observed outcome can reasonably be linked to the underlying unobservable probability as:

$$C_{ijt} = 1 \text{ if } C^* > 0 \text{ and } 0 \text{ otherwise}$$

Given the categorical nature of the dependent variables, Logit or Probit estimation is the most appropriate estimation approach. We utilize 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 among inspection outcomes exist in the robustness section of our empirical analysis.

3.2 Data

Data were obtained directly from the Food and Drug Administration (FDA) and represent manufacturing facility inspections under the responsibility of the Center for Drug Evaluation Research (CDER), which oversees both the evaluation of new drug products before they are approved to be sold and the safety and efficacy of drug products thereafter. CDER regulates prescription (Rx) and over-the-counter (OTC) drug products, as well as brand name and generic drug products, in an effort to ensure that the health benefits outweigh the known risks.

¹³ As with many multi-equation 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. Thus, 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.

Our main source of data is from 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 within the United States. We assembled data on every inspection conducted under CDER over a fourteen year period (1990-2003), which resulted in a sample of more than 10,000 inspections of roughly 2,400 manufacturing facilities. 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 our study, it is important to delineate changes in ownership structure. Fortunately the FDA requires that pharmaceutical manufacturing facilities selling drug products within the U.S. register with the agency. A registration and listing database maintained by FDA records the pharmaceutical firm (or firms) that owns each manufacturing facility in each year, the location of manufacturing establishments and the drug products manufactured. We created a corporate ownership database for each manufacturing facility using the FDA registration and listing database, correcting for any identifiable mismatches within the registration history records of these manufacturing facilities.

Working with the FDA, we also assembled a training database of all CDER investigators engaged in pharmaceutical manufacturing facility inspections before and during our study window. This database tracks all employer-sponsored training, both in terms of total courses taken and days spent in instruction. It also tracks the particular courses—those deemed focal and those deemed supplemental by FDA (discussed below)—that have been 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, using actual calendar dates between cGMP inspections for the manufacturing facilities in our sample. The variable *Days Between Inspection*

represents the number of days between inspections for a given manufacturing facility and characterizes our first dependent variable. Our second dependent variable captures the regulatory outcome of these inspections. *Inspection Outcome* ranges from a certification of complete compliance [labeled “no action indicated (NAIs)”], to mild noncompliance [labeled “voluntary action indicated (VAIs)”] and complete noncompliance [labeled “ordered action indicated (OAI)”].¹⁴ Given the qualitative differences between complete compliance (e.g., NAI), mild noncompliance (e.g., VAI) and complete noncompliance (e.g., OAI), we begin with OAI as our dependent variable but examine other permutations in our robustness analysis.

3.3.2 Independent Variables

Several FDA-specific factors are likely to affect the frequency and outcomes of manufacturing facilities inspections. One such factor is the reason for inspection, which falls into three distinct categories: (1) surveillance; (2) compliance; and (3) customer complaints. Surveillance inspections relate to a congressional mandate that FDA must make “regular and periodic” inspections of existing manufacturing facilities. *Surveillance* is a dummy variable that equals one if the reason for inspection is for regular and periodic cGMP surveillance, and is zero otherwise. A second reason for cGMP inspections is manufacturing facility compliance related to manufacturing process changes. Manufacturing facilities are required to notify the FDA of any changes they make to either an existing manufacturing processes or upon the establishment of a new manufacturing process. This notification provides information to the FDA that we anticipate will be used by FDA to alter inspection priorities. *Compliance* is a dummy variable that equals one if the FDA has received such notification by a manufacturing facility, and is zero otherwise. A third reason for cGMP inspections is from customer complaints. Customers (e.g., medical establishments) or retail consumers may have access to information that is unavailable to the FDA. A customer complaint inspection process encourages customers and/or consumers to reveal this information, which in turn the FDA may use to alter inspection priorities. *Customer Complaint* is a dummy variable that equals one if the reason for inspection is due to a customer

¹⁴ OAI compliance outcomes commonly include manufacturing facilities conducting voluntary recalls, but actions and/or sanctions can be more severe. Recommended OAI actions include banning; certification withholding or revocation; citation; civil penalty; disqualification; emergency permit disapproval; injunction; license denial, suspension, or revocation; prosecution; provisional listing; recall (FDA initiated recalls); recommendation for denial of pending application; recommendation for revocation of approved application; remove from shippers list; seizure/detention; use prohibited; warning letter; demand for destruction.

complaint, and is zero otherwise. We anticipate that the frequency of cGMP inspections is higher and the likelihood of cGMP violations is more likely in response to compliance and customer complaint inspections, in comparison to surveillance inspections (the omitted category in our empirical analysis).

Another factor that likely affects the frequency and outcomes of cGMP compliance inspections is the geographic location of manufacturing facilities. Manufacturing facilities within the U.S. are accounted for by regional fixed effects, while foreign inspections are accounted for by a dummy variable (*Foreign Inspection*) that equals one if the inspection is conducted outside of the U.S., and is zero otherwise. The potential for foreign inspections to evoke either a different time pattern of inspections or regulatory outcomes stems from the fact that foreign inspections are more costly than those conducted domestically and the fact that the personnel conducting these inspections are different in comparison to their domestic counterparts.¹⁵

In terms of the FDA inspection outcomes, the longer the time between cGMP inspections the greater is the information asymmetry gap and the more likely that manufacturing facilities will (conscientiously or unconscientiously) allow their processes to atrophy into noncompliance. Accordingly, we include *Days Between Inspection*, the natural logarithm of the days since the manufacturing facility was last inspected, in the inspection outcome econometric analysis.

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

¹⁵ Foreign pharmaceutical manufacturing facility inspections are normally undertaken by personnel based in the Office of Regulatory Affairs (ORA), instead of personnel based in the Center for Drug Evaluation Research (CDER).

its two prior inspections. We also proxy for information provided by changes to reputational status by accounting for whether the manufacturing facility has improved or deteriorated in cGMP compliance performance over its two prior inspections. *Improving Reputation* is a dummy variable equal to one if the most prior inspection of a manufacturing facility resulted in a finding of either complete compliance (i.e., received NAI) or mild noncompliance (i.e., received VAI) from a previous inspection of noncompliance (i.e., received OAI), and is zero otherwise. *Deteriorating Reputation* is a dummy variable set equal to one if the most prior inspection resulted in a finding of complete noncompliance (i.e., received OAI) from a previous inspection of either complete compliance (i.e., received NAI) or mild noncompliance (i.e., received VAI), and is 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 influences the probability of detecting noncompliance. We utilize three variables to capture the level of training of individual FDA investigators. *Main Courses* is a count of the number of drug courses deemed by the FDA as particularly important for conducting cGMP inspections that the investigator has completed prior to the focal cGMP inspection. These drug courses cover broad and general topics related to pharmaceutical manufacturing.¹⁶ *Supplemental Courses* is a count of the number of other courses that the investigator has completed prior to the focal cGMP inspection. These courses cover specialty topics in biology, pharmacology, manufacturing processes, among others. *Total Courses* is a count of the number of total (main and supplemental) drug courses the FDA investigator has completed prior to the focal cGMP inspection, and represents our initial measure of training in the econometric analysis. We nevertheless also examine the effects of the main 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 cGMP compliant manufacturing facilities versus cGMP noncompliant manufacturing facilities. *Cumulative Inspections* is the logged number of previous cGMP inspections conducted by the FDA investigator prior to focal cGMP inspection. Similar to the

¹⁶ Five drug courses are considered particularly important for FDA investigators in understanding cGMP regulations: (1) Basic Drug School; (2) Advanced Drug School; (3) Pre-Approval Inspections; (4) Active Pharmaceutical Ingredient (API) Manufacturing; and (5) Sterilization.

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 investigator experience and training impact inspection frequency and inspection outcomes, we also control for other potential determinants of these outcomes. The FDA views prescription (Rx) drug products as posing a higher potential for public safety and health consequences should there be manufacturing problems, in compared to over the counter (OTC) drug products (FDA, 2004). Whether the focal manufacturing facility produces prescription drug products may therefore be an important factor, particularly in choosing whether and when to inspect.

Several variables are included to capture manufacturing facility-specific characteristics, which might influence inspection frequency and outcomes. Drug products have different release profiles (e.g., extended release, delayed release, etc.) associated with their administration, which are dependent upon several technological parameters, including drug solubility, half life, protein binding, site of absorption, etc. 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 characteristics of a dose of medication, including such factors as appearance, form, product administration, dosage 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 sterile environments, as FDA views these environments as posing higher potential for public health consequences should there be drug defects (FDA, 2004). Finally, we control for the size of the manufacturing facilities in our sample. On the one hand, large manufacturing facilities face a greater likelihood of inspection. On the other hand, large facilities likely have superior manufacturing processes in place via scale and scope economies which subsequently improve cGMP compliance. *Products* represent the logged number of drug products produced within a manufacturing facility at the time of the focal cGMP inspection. Table 1 provides details on the construction of the control variables.

We also control for unmeasured variation that might exist from differences in FDA District Offices and FDA investigators, respectively, using fixed effects. There are twenty unique

FDA district offices (including headquarters) located regionally throughout the U.S. There are hundreds of FDA investigators who 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 (i.e., those with at least fifteen inspections completed). There are hundreds of manufacturing facilities that have been inspected at least once over the time period of our study. Similar to FDA investigators, we again confine our fixed effects analysis to those facilities that have received the most inspections (i.e., those with at least five inspections).

3.4 Summary Statistics

Our unit of observation is the “manufacturing facility inspection,” defined according to whether and when a manufacturing facility was inspected (i.e., inspection frequency), and if so, the outcome of that inspection (i.e., complete compliance, mild noncompliance or complete noncompliance). 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 technology variables represent non-exclusive categories. For example, a drug product inspected within a manufacturing facility might be for prescription (versus OTC), in a prompt release profile, and in soft gel cap dosage form. Moreover, the manufacturing facility itself might have several different release profiles or dosage forms in operation in a given facility-year. The control variables exhibit substantial heterogeneity. The FDA inspects a manufacturing facility roughly every 500 days on average, but substantial variation exists. The predominant cGMP inspection outcome is voluntary action indicated (43% VAI), although both no action indicated (38% NAI) and ordered action indicated (19% OAI) are well represented. Surveillance inspections are the most frequent (63%) reason for inspection, while compliance inspections are less frequent (37% of inspections) and customer complaint inspections (nearly 0%) are rare in comparison. Roughly 13 percent of cGMP inspections occur in foreign manufacturing facilities. Nearly two-thirds of the manufacturing facilities in our sample have a *Good Reputation* (i.e., are consistently compliant) with the FDA, while roughly eight percent of the manufacturing facilities have a *Bad Reputation* (i.e., are consistently noncompliant). Roughly 13 percent have a *Deteriorating Reputation* (i.e., have become noncompliant in the prior inspection), while this

same percentage obtains for *Improving Reputation* (i.e., have become compliant in the prior inspection). FDA investigators have completed on average roughly one training course (main or supplemental) prior to a cGMP inspection. Moreover, FDA investigators have completed, on average, nearly 17 cGMP inspections prior to a cGMP inspection. The investigator training and experience variables also exhibit substantial variation.

Table 3 provides correlation statistics for the dependent, independent and control variables. Longer time between cGMP inspections is positively associated with VAI outcomes, surveillance inspections, foreign inspections and good reputations, and negatively associated with OAI outcomes, compliance inspections and bad or deteriorating reputations. OAI inspection outcomes (i.e., complete noncompliance) are positively associated with compliance inspections and bad or deteriorating reputations, and negatively associated with surveillance inspections, foreign inspections, good reputations and investigator training and experience. VAI inspection outcomes (i.e., mild noncompliance) are positively associated with the number of days between inspection, foreign inspections, good or improving reputations and investigator training, and negatively associated with bad or deteriorating reputations.

3.5 Econometric Results

Tables 4 and 5 present the econometric results of inspection frequency and inspection outcome, respectively. Table 6 provides several robustness tests for the inspection outcome econometric analysis. All models presented easily reject likelihood ratio null hypothesis tests for the inclusion of fixed effects and the control and independent variables, at least at the 0.001 level. In both the inspection frequency and inspection outcome analyses, we adjust standard errors for robustness and within-manufacturing facility clustering. Due to the construction of some of our independent variables, we restrict the sample to those manufacturing facilities that receive at least two inspections. While this approach reduces modestly the number of observations available, between six and eight thousand observations (i.e., unique cGMP inspections) remain. The analyses include manufacturing facility-level covariates as controls, but the tables report only those variables germane to our analysis—namely the FDA inspection decision and FDA investigator training and experience variables.

3.5.1 Inspection Hazard Rate Results

Table 4 presents the results for the inspection frequency (i.e., event history) econometric analysis. Model 1 uses the exponential distribution model while Models 2 and 3 replicate the Model 1 results using the Gompertz and Cox Proportional hazard models, respectively. Individual coefficients across these models are nearly identical in magnitudes, signs and statistical significance. The A models of Table 4 represents a baseline, and include the manufacturing facility control variables and FDA District Office (DO) fixed effects. The B models add the FDA inspection decision variables related to the reason for inspection (i.e., compliance or customer complaint), foreign inspections, and manufacturing facility reputation to the A models. The C models add manufacturing facility (MF) fixed effects to the B models. We focus our discussion on the B and C model results.

Compliance inspections increase the hazard of inspection in all estimations ($p < 0.01$), indicating that FDA shortens the time between cGMP inspections when manufacturing facilities modify processes or establish new processes. The results indicate the hazard of inspection increases an average of roughly 20 percent as a consequence of a compliance-driven inspection, in comparison to a surveillance-driven inspection.¹⁷ Customer complaints reduce the time between inspections in all models ($p < 0.05$), while foreign manufacturing facilities increase the time between inspections in models without manufacturing facility fixed effects ($p < 0.01$). Neither of these results is surprising. The increased hazard of inspection attributable to customer complaints suggests that the FDA seeks to utilize information available to third parties (here, customers or consumers) as a vehicle to manage its under-endowment 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 B model results of Table 4 also indicate that manufacturing facilities with bad reputations ($p < 0.05$) or deteriorating reputations ($p < 0.05$) increase the hazard of inspection, in comparison to those with good reputations (our omitted category). These results suggest that the FDA actively relies upon information secured and reputations developed from prior inspections

¹⁷ We examine the probabilistic increase (or decrease) in the hazard (i.e., the probability of an inspection occurring in time $t+1$, given no inspection to time t) of inspection. The increase (or decrease) in the hazard of inspection for a particular variable is derived by taking the exponential of that coefficient (i.e., $\exp(\beta_i)$) at a particular value and dividing it by the exponential of the coefficient at another (i.e., base) value.

to allocate inspection resources. The estimations also reveal a dynamic quality to the way investigators use information secured from prior inspections. Specifically, all of the Table 4 models indicate that the FDA targets those facilities with deteriorating reputations for more frequent inspections ($p < 0.01$). Not only do we find statistical significance from these information/reputation variables, but the estimation results shed considerable light on the conduct of day-to-day regulation activities. For instance, by drawing on the estimated coefficients we find that manufacturing facilities with bad reputations face a hazard of inspection that is 13 percent greater in comparison to manufacturing facilities with good reputations, while manufacturing facilities with deteriorating reputations face a hazard of inspection that is 27 percent greater in comparison to manufacturing facilities with good reputations. The estimations reveal not only the importance of regulators' propensity to draw upon information from prior inspections, but also the costly regulatory consequences over time that manufacturing facilities bear from lapses in 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,¹⁸ which modestly reduces sample size in comparison to previous models. Compliance inspections and customer complaint inspections maintain their positive and statistically significant effects on inspection frequency, while the effect of foreign inspections on inspection frequency not surprisingly becomes insignificant. *Deteriorating Reputation* maintains its positive and statistically significant coefficient, while the effect of manufacturing facilities with bad reputations on inspection frequency loses its statistical significance.

3.5.2 Inspection Outcomes

As discussed above, FDA inspection frequency decisions are influenced by myriad factors. One of the most notable factors is the information developed from previous inspections that subsequently shape manufacturing facility reputations. We now turn to an exploration of whether these same determinants, as well as investigator training and experience, influence

¹⁸ Summary statistics confirm that manufacturing facilities with more than five inspections are essentially identical to manufacturing facilities with five or less inspections along the following dimensions: (1) facility-specific factors (e.g., dosage forms, release profiles); (2) inspection outcomes; (3) reasons for inspection; (4) facility reputation; and (5) investigator-specific factors. Some statistical differences do exist between these two sets of facilities, however, along the following dimensions: (1) prescription products (i.e., larger for > 5 inspections); (2) number of drug products manufactured (i.e., larger for > 5 inspections); (3) days between inspections (i.e., smaller for > 5 inspections); and (4) foreign inspections (i.e., smaller for > 5 inspections).

inspection outcomes. Table 5 presents the inspection outcome results, using OAI (i.e., complete noncompliance) as the dependent variable. Model 1 of Table 5 includes FDA District Office fixed effects and the manufacturing facility-specific control variables. Model 2 adds the set of FDA inspection decision variables to Model 1, while Model 3 adds the set of FDA investigator experience and training variables to Model 1.¹⁹ 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 overall estimation results are very encouraging. The likelihood of noncompliance increases as the number of days between cGMP inspections increases ($p < 0.05$) in all models. Two possible (and not necessarily competing) explanations arise from this result. First, manufacturing facilities may be more likely to let their manufacturing processes atrophy into noncompliance with the passage of time.²⁰ Second, investigators who are aware of a longer period between inspections may more thoroughly scrutinize the focal manufacturing facility. Regardless of whether the first, second or some combination of these explanations is driving this result, it suggests the information signal provided by *Days Between Inspection* is a predictor of regulatory outcomes.

The empirical results indicate that manufacturing facilities inspected for reasons of *Compliance* are significantly more likely to be found noncompliant than those facilities inspected for reasons of regular and periodic surveillance ($p < 0.01$) in all models. This result suggests that

¹⁹ A potential confound arises if inspectors are linked in a systematic fashion to particular facilities. With limited exceptions, however, the FDA randomizes inspectors to the facilities they inspect. In this regard, it is also important to note that FDA management, rather than the inspectors themselves, make the decision of which facilities to inspect 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 (e.g., follow-up inspections), it is sensible for the same FDA investigator to inspect the same manufacturing facility, especially if the facility was previously found non-compliant. Thus, some regularity of inspections by individual regulators of particular facilities is expected. To explore this, we empirically examined the repetition of individual regulator inspections of specific manufacturing facilities. The results indicate that only 14.5% of the time does the same regulator visit the same manufacturing facility for two consecutive inspections, and this condition falls to 4.4% and 1.8%, respectively, for three and four consecutive inspections. Manufacturing facilities that receive more inspections are also visited by more and different FDA investigators. The pair-wise correlation coefficient between the number of manufacturing facility inspections and the number of distinct FDA investigators is 0.90.

²⁰ Note that while the passage of time allows, *ceteris paribus*, for degradation in the likelihood of compliance a second and separate effect (as identified empirically in Table 4) is that, contingent on the outcome of a given inspection, the greater the compliance of the manufacturing facility, the longer the time before the FDA re-inspects the manufacturing facility.

regulators seek to close the information asymmetry gap by drawing upon the information provided by manufacturing facilities when those facilities signal a change in their manufacturing processes. Given that all new processes are subject to some additional compliance uncertainty, this heightened uncertainty is likely to help explain why compliance rates for compliance-driven inspections are reduced.²¹ While *Customer Complaints* significantly shorten inspection frequency, we find that this variable does not have a statistically significant impact on inspection compliance. These findings plausibly suggest that while the FDA utilizes customer complaints as an information signal regarding inspection targets, the information content of that signal is relatively weak. Finally, the results reveal no robust statistically significant effect of foreign facilities being found in serious violation, in comparison to their domestic counterparts. We return to this result in our robustness section.

The Table 5 results provide strong support for the importance of the individual reputation variables. Manufacturing facilities with bad reputations are significantly more likely to be found in violation of cGMP regulations ($p < 0.05$) in all models. Manufacturing facilities with either improving reputations ($p < 0.01$) or deteriorating reputations ($p < 0.01$) are significantly more likely to be found completely noncompliant than manufacturing facilities with good reputations. These results provide strong evidence that the FDA draws upon information of prior regulatory lapses in current inspections. The economic interpretation of these results is also interesting. We find that the likelihood of manufacturing facilities with *Bad*, *Deteriorating* and *Improving Reputations* found seriously noncompliant increases (relative to manufacturing facilities with *Good Reputations*) by roughly 134%, 62% and 22%, respectively, using the coefficients from the reputation parameters in Model 4.

The results also indicate statistically significant effects associated with inspector experience. In particular, the statistical significance of *Cumulative Inspections* ($p < 0.05$) in all models suggests that the information accumulated over time by individual investigators significantly influences the likelihood of finding manufacturing facilities out of compliance. In particular, we find investigator experience reduces the likelihood of finding a manufacturing facility out of compliance. We also find that investigators who have received more training are

²¹ If compliance inspections that identify compliance failures are met with corrective actions by firms, then subsequent compliance rates identified through standard surveillance inspections may be similar to (or even better than) the population of other inspections.

similarly less likely to find manufacturing facilities noncompliant (although the results are not statistically significant in all estimations). We return to both of these results immediately below.

Model 5 and Model 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 ten cGMP inspections and those manufacturing facilities that have received at least five inspections, respectively. The results of these models are broadly consistent across 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. All of 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 whether any nonlinear effects exist from either investigator experience or investigator training on inspection outcomes via the inclusion of squared terms. The Model 2 results 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 noncompliant. *Ceteris paribus*, we find that the likelihood of non-compliant outcomes peaks for investigators with roughly ten inspections. This u-shaped pattern holds for investigator training as well. In particular, investigators with relatively limited or relatively significant training via the number of main and supplemental drug courses taken reduce the likelihood of manufacturing facilities being found noncompliant, while more modestly trained investigators increase this probability.

Model 3 examines whether greater specificity in the types of courses taken by FDA investigators influence cGMP inspection outcomes of manufacturing facilities. Recall that our data track the number of focal drug courses (i.e., general pharmaceutical manufacturing topics) and supplemental drug courses (i.e., specialty topics). The Model 3 results indicate that *Supplemental Courses* provide certain benefits to investigators in understanding cGMP noncompliance, in comparison to *Main Courses*.

Models 4-6 of Table 6 replicate the Models 1-3 results of Table 6, respectively, using VAI in place of OAI as the dependent variable. These models reinforce our earlier finding that

Days Between Inspections is a significant determinant of regulatory outcomes. Manufacturing facilities inspected for reasons of compliance, however, are not more likely to be found mildly noncompliant than facilities under general surveillance. Interestingly, foreign manufacturing facilities are significantly more likely ($p < 0.01$) to be found mildly noncompliant than domestic manufacturing facilities across all models. The Models 4-6 results provide some nuanced insights into inspection outcomes regarding manufacturing facility reputations. Recall from Table 5 that manufacturing facilities with bad reputations are found more likely to receive an OAI outcome on any given inspection (i.e., found completely noncompliant). Here, manufacturing facilities with bad reputations are found less likely to receive VAI outcomes ($p < 0.01$), in comparison to manufacturing facilities with good reputations in all models. The reason for this result is that manufacturing facilities with bad reputations are more likely to be found completely noncompliant (i.e., receive an OAI). Moreover, while deteriorating reputations increases the likelihood of OAI inspection outcomes, *Deteriorating Reputation* reduces the likelihood of receiving VAI outcomes ($p < 0.05$) in all models. The results of investigator experience and training on VAI inspection outcomes are also interesting. Model 4 indicates that more experienced FDA investigators are generally less likely to find manufacturing facilities mildly noncompliant (but statistical significance is not achieved in all models), while FDA investigators with more training are more likely ($p < 0.05$) in some models. The former result is in contrast with the Table 5 results using OAI as the dependent variable. Model 5 of Table 6 indicates no statistically significant nonlinear effects from investigator cumulative inspection experience and total drug courses taken. Model 6 of Table 6 shows that *Main Courses* ($p < 0.10$) and *Supplemental Courses* ($p < 0.05$) increase the probability that manufacturing facilities receive VAI inspection outcomes—a result in contrast to the Model 3 results of Table 6 using OAI as the dependent variable.

We also examined but do not report three empirical robustness tests. In the first unreported robustness test, we replaced the probit estimation with multinomial logit estimation, using no action indicated (NAI) as the base category and recognizing that assumptions of independence and specific cardinal ordering among alternative outcomes can be questioned. The results not surprisingly follow the Models 1-6 results presented in Table 6. In the second unreported robustness test, we replaced the probit estimation with ordered probit estimation. This estimation approach presumes an ordering—increasing in severity from NAI, to VAI and then

OAI—exists among inspection outcomes. The results are also strongly similar to our earlier probit models. In particular, all of the FDA inspection decision variables and FDA investigator variables maintain statistical significance. In the final unreported robustness test, we alter our reputation variables using a one-period lag structure as opposed to our two-period lag structure.²² In this setting, we specify manufacturing facilities with bad reputations as those that received an OAI in the most previous inspection, while manufacturing facilities with good reputations are those that received an NAI in the most previous inspection. The base case reputation, which is neither improving nor deteriorating, is a VAI outcome. The unreported results indicate that facilities with bad reputations are more likely to be inspected ($p < 0.01$), while facilities with good reputations are statistically less likely ($p < 0.05$) to be inspected.

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. Rather both the frequency and regulatory stringency of inspections are influenced by systematic efforts of regulators to take advantage of alternative means to narrow the information asymmetry gap. Our examination of the regulatory decision to inspect manufacturing facilities for cGMP compliance indicates that regulators draw upon 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 based on the source of the inspection prompt. While regulators may seem to simply go about their business as a result of statutory requirements to inspect manufacturing facilities, our estimations indicate that they also use cues from both the manufacturing facilities themselves (e.g., process change notices) and consumers and customers (e.g., complaints) to alter their inspection behaviors.

Regulators also seek to overcome the information asymmetry gap by drawing upon data gathered from inspections. In particular, regulators draw upon information secured through previous inspections to form heuristic reputations of manufacturing facilities that, in turn, are used to guide and influence regulatory decisions. A previously earned reputation as “good” manufacturing facility is met with more of a regulatory “hands off” approach, while a

²² 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 subjective at best.

manufacturing facility with a previously earned reputation as a regulatory “bad boy” is found to be scrutinized more thoroughly. This result is especially telling as it indicates that in the face of regulators’ inability to detect certain relevant features of the facility (e.g., whether the facility’s management is sloppily seeking to skate by in its manufacturing process or that the facility’s physical infrastructure imposes undue risks), regulators find a way to narrow, if even imperfectly, the information asymmetry gap.

Second, the time span and breadth of panel data we have employed permit us to identify the importance of FDA regulators’ experience and training (i.e., information accumulation) as determinants of regulatory outcomes. The more inspections conducted by an FDA investigator prior to a focal manufacturing facility inspection, the greater the decrease in probability that the investigator will issue a cGMP noncompliant outcome. To place an economic interpretation on this finding we utilize the Model 4 results of Table 5 to estimate the difference in the probability of an OAI outcome for investigators with one standard deviation more cGMP inspection experience (roughly 22 inspections) from the mean level of cGMP inspection experience (roughly 24 inspections). Investigators with one standard deviation more cGMP inspection experience are roughly two percent less likely to find manufacturing facilities noncompliant in comparison to the mean level of investigator cGMP 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, as well as FDA inspection decision variables, we find that the likelihood of facilities 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 impact that FDA regulators have, we utilize Model 5 in Table 5 to estimate the increase in the probability of an OAI outcome by investigators and then display a histogram of the distribution of these probabilities in Figure 1. 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) percent. This analysis establishes an empirical regularity even after accounting for human

capital accumulation through training and experience; FDA regulators (i.e., investigators) are markedly heterogeneous.²³

4 CONCLUSION

Over the past two decades increasing theoretical sophistication has been brought to the modeling of the relationship between regulators and the firms they regulate. A principal 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, in turn, has 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 under-explored aspect of the information asymmetry gap; namely, 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 regulators utilize previously secured information in guiding regulatory (inspection) decisions. Additionally, we explore the role that regulator experience and training (along with a host of other controls) has in affecting regulatory outcomes. Our analysis incorporates a rich panel dataset 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 utilize information secured from prior interactions with manufacturing facilities, and engage in training of inspectors 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 regulator-regulated firm interaction are likely to benefit from incorporating regulators' efforts at overcoming information asymmetries. Our

²³ While our data include granular information on each inspection along with detailed information on investigator experience and training, data on individual compensation and reward mechanisms for individual inspectors was unattainable. Based on conversations with FDA management, our understanding is that inspector compensation has no direct or indirect tie to inspection outcomes. We were also unable to obtain other information on individual investigators, such as age, race, gender, etc.

analysis also point toward an important reality of regulator heterogeneity that is in need of greater exploration.

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Table 1: Variable Definitions

CONTROLS	DEFINITION
<i>Prescription</i>	Dummy variable indicating facility manufactures prescription drug products
<i>Prompt Release</i>	Dummy variable indicating facility manufactures drug products with prompt release profiles
<i>Ext./Del. Release</i>	Dummy variable indicating facility manufactures drug products with extended/delayed release profiles
<i>Gel Cap</i>	Dummy variable indicating facility manufactures drug products in gel cap dosage forms
<i>Soft Gel Cap</i>	Dummy variable indicating facility manufactures drug products in soft gel cap dosage forms
<i>Ointment</i>	Dummy variable indicating facility manufactures drug products in ointment dosage forms
<i>Liquid</i>	Dummy variable indicating facility manufactures drug products in liquid dosage forms
<i>Powder</i>	Dummy variable indicating facility manufactures drug products in powder dosage forms
<i>Gas</i>	Dummy variable indicating facility manufactures drug products in gas dosage forms
<i>Parenteral</i>	Dummy variable indicating facility manufactures drug products in parenteral dosage forms
<i>LV Parenteral</i>	Dummy variable indicating facility manufactures drug products in large volume parenteral dosage forms
<i>Aerosol</i>	Dummy variable indicating facility manufactures drug products in aerosol dosage forms
<i>Bulk</i>	Dummy variable indicating facility manufactures drug products in bulk dosage forms
<i>Suppository</i>	Dummy variable indicating facility manufactures drug products in suppository dosage form
<i>Sterile</i>	Dummy variable indicating facility manufactures sterile drug products
<i>Products</i>	Logged count of the number of distinct drug products the facility manufactures
INDEPENDENT	DEFINITION
<i>Good Reputation</i>	Facility received (NAI, NAI), (NAI, VAI), (VAI, NAI) or (VAI, VAI) in two prior inspections
<i>Bad Reputation</i>	Facility received (OAI, OAI) in two prior inspections
<i>Deteriorating Reputation</i>	Facility received (NAI, OAI) or (VAI, OAI) in two prior inspections
<i>Improving Reputation</i>	Facility received (OAI, VAI) or (OAI, NAI) in two prior inspections

Table 2: Summary Statistics

VARIABLE	MEAN	SD	MIN	MAX	VARIABLE	MEAN	SD	MIN	MAX
DEPENDENT VARS					CONTROL VARS				
<i>Inspection Frequency</i>	489.07	513.90	1.00	4830.00	<i>Prescription</i>	0.67	0.47	0.00	1.00
<i>No Action Indicated (NAI)</i>	0.38	0.49	0.00	1.00	<i>Prompt Release</i>	0.20	0.40	0.00	1.00
<i>Voluntary Action Indicated (VAI)</i>	0.43	0.49	0.00	1.00	<i>Extended/Delayed Release</i>	0.07	0.25	0.00	1.00
<i>Ordered Action Indicated (OAI)</i>	0.19	0.39	0.00	1.00	<i>Gel Cap</i>	0.07	0.26	0.00	1.00
					<i>Soft Gel Cap</i>	0.01	0.10	0.00	1.00
					<i>Ointment</i>	0.07	0.26	0.00	1.00
INSPECTION DECISION VARS					<i>Liquid</i>	0.16	0.36	0.00	1.00
<i>Days Between Inspections</i>	5.57	1.30	0.69	8.48	<i>Powder</i>	0.03	0.16	0.00	1.00
<i>Surveillance</i>	0.63	0.48	0.00	1.00	<i>Gas</i>	0.00	0.03	0.00	1.00
<i>Compliance</i>	0.37	0.48	0.00	1.00	<i>Parenteral</i>	0.12	0.33	0.00	1.00
<i>Customer Complaint</i>	0.00	0.05	0.00	1.00	<i>LV Parenteral</i>	0.01	0.10	0.00	1.00
<i>Foreign Inspection</i>	0.13	0.34	0.00	1.00	<i>Aerosol</i>	0.01	0.11	0.00	1.00
<i>Good Reputation</i>	0.66	0.47	0.00	1.00	<i>Bulk</i>	0.16	0.37	0.00	1.00
<i>Bad Reputation</i>	0.08	0.27	0.00	1.00	<i>Suppository</i>	0.01	0.09	0.00	1.00
<i>Improving Reputation</i>	0.13	0.33	0.00	1.00	<i>Sterile</i>	0.04	0.20	0.00	1.00
<i>Deteriorating Reputation</i>	0.13	0.34	0.00	1.00	<i>Products</i>	2.70	1.22	0.69	5.16
INVESTIGATOR VARS									
<i>Cumulative Inspections</i>	2.81	0.98	0.69	5.02					
<i>Main Courses</i>	0.58	0.83	0.00	4.00					
<i>Supplemental Courses</i>	0.38	0.74	0.00	5.00					
<i>Total Courses</i>	0.96	1.12	0.00	6.00					

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) No Action Indicated (NAI)	-0.02	1.00															
(3) Voluntary Action Indicated (VAI)	0.05	-0.68	1.00														
(4) Ordered Action Indicated (OAI)	-0.05	-0.38	-0.42	1.00													
(5) Days Between Inspections	0.80	-0.04	0.06	-0.02	1.00												
(6) Surveillance	0.16	0.11	0.02	-0.17	0.12	1.00											
(7) Compliance	-0.16	-0.11	-0.02	0.17	-0.12	-0.99	1.00										
(8) Customer Complaint	-0.02	0.00	-0.01	0.00	-0.02	-0.07	-0.04	1.00									
(9) Foreign Inspection	0.21	-0.05	0.08	-0.05	0.19	0.03	-0.03	-0.02	1.00								
(10) Good Reputation	0.08	0.12	0.04	-0.20	0.03	0.23	-0.23	0.00	0.00	1.00							
(11) Bad Reputation	-0.06	-0.09	-0.07	0.20	-0.03	-0.17	0.17	-0.01	-0.03	-0.40	1.00						
(12) Improving Reputation	0.03	-0.03	0.03	0.01	0.02	-0.03	0.03	0.01	0.02	-0.54	-0.11	1.00					
(13) Deteriorating Reputation	-0.09	-0.07	-0.02	0.12	-0.05	-0.16	0.16	-0.01	0.00	-0.55	-0.11	-0.15	1.00				
(14) Cumulative Inspections	0.10	0.02	0.00	-0.03	0.13	0.01	-0.01	-0.03	0.18	-0.01	0.00	0.01	0.00	1.00			
(15) Main Courses	0.15	-0.02	0.03	-0.01	0.15	-0.01	0.01	-0.02	0.00	-0.01	0.02	0.01	-0.01	0.28	1.00		
(16) Supplemental Courses	0.02	-0.01	0.03	-0.03	0.04	0.00	0.00	-0.01	0.06	0.01	0.00	0.00	-0.02	0.16	0.02	1.00	
(17) Total Courses	0.12	-0.03	0.04	-0.02	0.13	0.00	0.01	-0.02	0.04	0.00	0.01	0.01	-0.02	0.31	0.75	0.67	1.00

Bold indicates pair-wise significance at 0.05 level

Table 4: Inspection Frequency Results

	Model 1A	Model 1B	Model 1C	Model 2A	Model 2B	Model 2C	Model 3A	Model 3B	Model 3C
<i>FIXED EFFECTS</i>	DO	DO	DO MF	DO	DO	DO MF	DO	DO	DO MF
<i>CONTROL VARS</i>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<i>Constant</i>	-6.98*** (0.05)	-6.99*** (0.06)	-6.96*** (0.39)	-6.90*** (0.05)	-6.94*** (0.05)	-6.99*** (0.40)			
<i>Gamma</i>				0.00*** (0.00)	0.00*** (0.00)	0.00** (0.00)			
<i>Compliance</i>		0.20*** (0.03)	0.15*** (0.03)		0.20*** (0.03)	0.16*** (0.03)		0.21*** (0.03)	0.16*** (0.03)
<i>Customer Complaint</i>		0.49** (0.21)	0.62** (0.28)		0.48** (0.21)	0.66** (0.29)		0.34* (0.19)	0.50** (0.26)
<i>Foreign Inspection</i>		-0.23*** (0.04)	0.93** (0.39)		-0.26*** (0.04)	-0.93** (0.39)		-0.22*** (0.04)	-1.31*** (0.23)
<i>Bad Reputation</i>		0.12** (0.05)	0.08 (0.06)		0.13*** (0.05)	0.07 (0.06)		0.12** (0.05)	0.07 (0.06)
<i>Improving Reputation</i>		-0.01 (0.03)	0.03 (0.04)		-0.01 (0.03)	0.02 (0.04)		-0.04 (0.03)	0.00 (0.04)
<i>Deteriorating Reputation</i>		0.24*** (0.03)	0.17*** (0.04)		0.25*** (0.03)	0.16*** (0.04)		0.23*** (0.03)	0.14*** (0.04)
Number of observations	7858	7858	6033	7858	7858	6033	7858	7858	6033
Wald (χ^2)	1927.8***	1392.7***	2764.1***	1179.8***	1609.7***	2598.7***	1723.7***	2268.4***	2613.1***
Log pseudo-likelihood	3764.5	3340.5	5153.3	3691.9	3794.2	5159.3	-51363.6	-51274.3	-35381.5
Estimation	Exponential	Exponential	Exponential	Gompertz	Gompertz	Gompertz	Cox	Cox	Cox

*** p<0.01 ** p<0.05 * p<0.10.

Fixed Effects: DO = FDA District Office; MF = Manufacturing Facility.

Table 5: Inspection Outcome Results

	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5	MODEL 6
<i>FIXED EFFECTS</i>	DO	DO	DO	DO	DO I	DO MF
<i>CONTROL VARS</i>	Yes	Yes	Yes	Yes	Yes	Yes
<i>Constant</i>	-0.87*** (0.08)	-1.31*** (0.12)	-0.68*** (0.10)	-1.17*** (0.13)	-1.09 (0.71)	-0.21 (1.14)
<i>Days Between Inspection</i>		0.02** (0.01)		0.03** (0.01)	0.06*** (0.02)	0.09*** (0.02)
<i>Compliance</i>		0.32*** (0.04)		0.33*** (0.04)	0.31*** (0.04)	0.29*** (0.05)
<i>Customer Complaint</i>		0.14 (0.28)		0.10 (0.28)	0.17 (0.28)	-0.06 (0.38)
<i>Foreign Inspection</i>		-0.04 (0.06)		-0.02 (0.06)	-0.11 (0.07)	-0.46 (1.34)
<i>Bad Reputation</i>		0.84*** (0.06)		0.85*** (0.06)	0.78*** (0.06)	0.17** (0.08)
<i>Improving Reputation</i>		0.20*** (0.05)		0.20*** (0.05)	0.18*** (0.06)	-0.21*** (0.07)
<i>Deteriorating Reputation</i>		0.48*** (0.05)		0.48*** (0.05)	0.47*** (0.06)	0.05 (0.06)
<i>Cumulative Inspections</i>			-0.05** (0.02)	-0.05*** (0.02)	-0.07** (0.03)	-0.09*** (0.03)
<i>Total Courses</i>			-0.07* (0.04)	-0.08** (0.04)	-0.10* (0.06)	-0.09* (0.05)
Number of observations	7858	7858	7858	7858	6480	4885
Wald (χ^2)	153.3***	635.8***	161.5***	664.7***	742.7***	768.9***
Pseudo-R ²	0.026	0.086	0.028	0.086	0.147	0.141
Log likelihood	-3765.7	-3543.5	-3756.6	-3533.7	-2811.6	-2351.6
Dependent Variable	OAI	OAI	OAI	OAI	OAI	OAI
Estimation	Probit	Probit	Probit	Probit	Probit	Probit

*** p<0.01 ** p<0.05 * p<0.10.

Fixed Effects: DO = FDA District Office; I = Investigator; MF = Manufacturing Facility.

Table 6: Inspection Outcome Robustness Results

	MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5	MODEL 6
<i>FIXED EFFECTS</i>	DO	DO	DO	DO	DO	DO
<i>CONTROL VARS</i>	Yes	Yes	Yes	Yes	Yes	Yes
<i>Constant</i>	-1.17*** (0.13)	-0.73*** (0.22)	-1.26*** (0.14)	-0.10 (0.12)	-0.28 (0.19)	-0.05 (0.12)
<i>Days Between Inspection</i>	0.03** (0.01)	0.03** (0.02)	0.04** (0.02)	0.03** (0.01)	0.04*** (0.01)	0.03** (0.01)
<i>Compliance</i>	0.33*** (0.04)	0.33*** (0.04)	0.34*** (0.04)	0.00 (0.03)	0.00 (0.03)	0.01 (0.03)
<i>Customer Complaint</i>	0.10 (0.28)	0.09 (0.31)	0.09 (0.27)	-0.14 (0.29)	-0.28 (0.29)	-0.44 (0.32)
<i>Foreign Inspection</i>	-0.02 (0.06)	-0.09 (0.06)	-0.05 (0.06)	0.27*** (0.05)	0.22*** (0.05)	0.24*** (0.05)
<i>Bad Reputation</i>	0.85*** (0.06)	0.87*** (0.06)	0.87*** (0.06)	-0.29*** (0.06)	-0.25*** (0.06)	-0.26*** (0.06)
<i>Improving Reputation</i>	0.20*** (0.05)	0.20*** (0.05)	0.21*** (0.05)	0.00 (0.05)	0.02 (0.05)	0.01 (0.05)
<i>Deteriorating Reputation</i>	0.48*** (0.05)	0.49*** (0.05)	0.52*** (0.05)	-0.10** (0.05)	-0.14*** (0.05)	-0.12*** (0.05)
<i>Cumulative Inspections</i>	-0.05*** (0.02)	-1.78*** (0.57)	-0.05** (0.02)	-0.04** (0.02)	0.65 (0.48)	-0.03* (0.02)
<i>Cumulative Inspections²</i>		0.80*** (0.26)			-0.32 (0.22)	
<i>Total Courses</i>	-0.08** (0.04)	-0.10** (0.04)		0.06*** (0.01)	0.02 (0.03)	
<i>Total Courses²</i>		0.02** (0.01)			0.01 (0.01)	
<i>Main Courses</i>			-0.04 (0.04)			0.03* (0.02)
<i>Supplemental Courses</i>			-0.11** (0.05)			0.06** (0.02)
Number of observations	7858	7858	7858	7858	7858	7858
Wald (χ^2)	664.7***	652.4***	711.8***	246.0***	248.6***	228.3***
Pseudo-R ²	0.086	0.087	0.083	0.025	0.027	0.024
Log likelihood	-3533.7	-3490.4	-3459.7	-5233.0	-5227.8	-5243.3
Dependent Variable	OAI	OAI	OAI	VAI	VAI	VAI
Estimation	Probit	Probit	Probit	Probit	Probit	Probit

*** p<0.01 ** p<0.05 * p<0.10.

Fixed Effects: DO = FDA District Office.

Figure 1: Distribution of Investigator Probabilities of Finding Noncompliance

