SUSTAINABILITY AND STRATIFIED NONCOMPLIANCE IN THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

The emerging field of strategic sustainability tracks the impact of corporate performance on profits, people and place (environment). Applying this model to the pharmaceutical industry, this paper examines patterns of non-compliance, particularly in regards to product safety (people). This paper explores a key performance indicator (KPI) metrics model for use in a Decision Support System (DSS) to track several major areas of non-compliance. A breakdown of warning letters issued by FDA inspector offices in recent years provides insight into the limitations of non-compliance metrics currently used by the FDA to enforce oversight. The FDA's effectiveness to police non-compliance is undermined by their lack of funding and reactivity, rather than proactive approaches, such as the application of metrics on the supply chain level of analysis. Final investigation shows that regulatory oversight should be proportional to potential profitability of an organization given that larger pharmaceutical companies have more sophisticated supply chain infrastructures which can be used to offload non-compliance risk. Implications are further discussed.

INTRODUCTION

Strategic sustainability argues that effective corporate performance must balance the legitimate needs of owner/investors, customers/communities, and the environment over the entire product class lifecycle in order to be considered sustainable (Borland, 2009; Presley, Meade & Sarkis, 2007). While the pharmaceutical industry is legendary for returning profits to its owner/investors, performance concerning lifecycle sustainability for customers and communities remains controversial. The issue of pharmaceutical noncompliance, or the act of a pharmaceutical company not following societal laws and regulations, has become an increasing problem in recent years. In terms of product safety, while the FDA has a variety of metrics available to track enforcement, political influence and under-funding hampers its efforts. Given these mediating variables are unlikely to change, this paper explores the nature of non-compliance and presents a targeted enforcement model to maximize effective resource allocation.

PHARMACEUTICAL INDUSTRY SUSTAINABILITY

Pharmaceuticals rank among the most lucrative of products. The distributors and wholesalers of pharmaceutical products pulled in revenues of over $340 billion in 2011 (Fein, 2012) and are expected to grow to over $400 billion within three years (WHO, 2014). The 10 largest drug companies control over one-third of this market, with profit margins of approximately 30% (WHO, 2014). The contract research industry posted $21.4 billion in revenue in 2010 (Mansell, 2012), while contract manufacturing facilities are estimated to reach revenues of $64 billion per year by 2016 (ASDReports, 2012).

The manufacture of pharmaceuticals involves the large match manufacture of "fine" chemicals with huge potential environmental impacts. The organic, inorganic, and synthetic processes involved are extraordinarily complex, making green impact comparative analyses of manufacturing methods very difficult, leading to controversies over what metrics to use and their accuracy as evidence of environmental sustainability (Yang et al., 2013). A more comprehensive lifecycle perspective involves an analysis of resources, materials, processing, cleaning, renewability, and disposal (Jiménez-González, Constable, & Ponder, 2012), accompanied by similar disputes over whether common metrics are too simplistic to accurately measure the environmental impact of fine chemical batch processing (Cirzons et. al., 2001; Watson, 2012). The environmental consequences of pharmaceutical compounds and manufacturing products disposal — as well as supply chain discharge of the same into the environment—is of particular concern (Pandya Amit, & Mavani Prati, 2012). This has led to an explosion of interest in "green chemistry" with accompanying claims of sustainability by pharmaceutical firms. Lilly, for example, has an award winning green pharmacy program addressing seven lifecycle stages:

- Research and Development
- Materials and natural resources
- Manufacturing
- Sales and Marketing
- Product transportation and packaging
- Product use
- Product end-of-life (Lilly, 2014)

However, critics allege the stellar economic performance of many pharmaceutical companies has come at the expense of the environment. Some firms base their claims of corporate sustainability on superficial changes that have minimal real environmental impact, such as trivial changes in product packaging (Singleton, 2013). Others are accused of regarding sustainability as just another formal requirement in the annual report, and putting a positive spin on selective metrics accordingly. In some cases tracking sustainability with inadequate metrics becomes a necessary foundation for positive public relations and the appearance of accountability (Marquis & Toffel, 2011; Schneider, Wilson & Rosenbeck, 2010). As Du summarizes: "Many firms advertise that they follow environmentally friendly practices to cover their true activities, a practice called greenwashing, which can cause the public to doubt the sincerity of greenization messages" (Du, 2015, p. 107). This paper will not explore environmental non-compliance in this area until a clear consensus emerges concerning tracking metrics, compliance standards, and methods of enforcement.

This same "greenwashing" mentality also threatens the people and community aspect of sustainability. Given the gravity of pharmaceutical noncompliance on large numbers of patients, this dimension of sustainability will be the focus of this paper. Every few months there seems to be another press release regarding a pharmaceutical company reaching a settlement for an exorbitant amount of money because of illegal marketing tactics, safety blunders or hidden research findings, in no small part due to inadequate or misleading metrics. In an effort to explain the rationale behind this "epidemic," an industry analysis will be performed for the pharmaceutical industry as a whole.

Given the inherent conflict of interest between corporate profit and public safety, the pharmaceutical and biotechnology fields are some of the most strictly regulated industries in the United States, as well as the rest of the world because of the public health issues involved—lives are literally at stake. With thousands of regulations covering areas such as nonclinical laboratory studies, marketing materials, and product labeling, the resources required to comply with the regulations are significant (Hale, Borys, & Adams, 2011). A widely accepted estimate for the cost of bringing a drug to market from start to finish is roughly $800 million to $1 billion (Harper, 2012). However, including the research and development spending of 12 of the largest pharmaceutical companies between 1997 and 2011, and the number of approved medicines within that time frame, reveals a cost of $4 to $11 billion per drug (Harper, 2012).

The U.S.Food and Drug Administration (FDA) asserts that regulations are necessary to ensure the products that are sold to the public are safe and effective. The Department of Justice Assistant Attorney General Tony West has publicly stated that the mission of the government is to dispel the myth that fines and civil lawsuits are just a cost of doing business (West, 2011). The FDA argues only regulatory oversight offsets the corrupting effect of corporate profit motive, which creates conflicts of interest between corporations and public health (Braithwaite, 2013; Gagnon, 2013). Given the enormous costs of drug development and approval, researchers note that corporations have a vested interest to maximize marketing, distribution and sales over emergent product safety issues, certainly until the R&D investment cost has been recouped (Brezis & Wiist, 2011; Mintzes, et. al., 2013). These pressures are intensified as the product patents approach their expiration date, allowing generic drug companies to create "bioequivalent" knockoffs at a fraction of the cost.

Politics and Resource Constraints

It is clear that, as with any other industry, politics play a large factor in the FDA's decision-making process. In 2009, the FDA plainly admitted that "four New Jersey congressmen and its own former commissioner unduly influenced the process that led to its decision last year to approve a patch for injured knees" (Harris & Halbfinger, 2009). The FDA went on to say that although they had not approved the product on multiple occasions, the persistent pressure of the legislators, who had considerable campaign contributions from the makers of the product, was too great and the scientific bodies that renounced the product were overruled. A recent study taken by members of the Union of Concerned Scientists noted that "One in four participants answered yes when asked, 'Have you ever been pressured to approve or recommend approval for

a device or product despite reservations about the safety, efficacy or quality of the product?'" (Spencer, 2012). Not only political pressure, but budgetary constraints can only allow the FDA to review so much data and to inspect so many facilities in an attempt to keep the American people safe from faulty drugs and devices. Consequently, the FDA had petitioned for a budget just shy of $4.5 billion dollars for fiscal year 2013, an increase of over $650 million from the previous fiscal year (FDA, 2012). By all accounts, they only received $3.9 billion; falling far short of funds they feel necessary to perform their job at the highest of levels (Mercola, 2013).

Non-Compliance Metrics

Regulatory non-compliance stems from: (i) compliance being too costly (Hale, Borys & Adams, 2011; Malhorta, 2012), (ii) "regulatory ambiguity" (Clifford, 2009), and (iii) risk-based assessment leading to regulatory defiance (Braithwaite, 2013; Gagnon, 2013). Motives for noncompliance are rarely mutually exclusive, with many variables entering the equation. In an effort to quantify the incidence of noncompliance and the implications that noncompliant behavior poses to the industry, a set of research methods have been devised. Table 1 shows the different agencies and the data they gather to quantify noncompliance.

TABLE 1: FEDERAL METRICS BY AGENCY

Agency	Data
U.S. Food and Drug Administration (U.S.FDA), Center for Drug Evaluation and Research (CDER)	Inspectional Observation (483), Warning Letter, Untitled Letter
U.S. Department of Justice (U.S.DOJ)	Criminal and Civil Litigation and Settlements
U.S. Department of Health and Human Services, Office of Inspector General (HHS OIG)	Corporate Integrity Agreement (CIA)

The U.S.FDA CDER issues Warning Letters, Untitled Letters, and Inspectional Observations for noncompliance based on information obtained from (1) findings during facility inspections, (2) marketing and advertising material review, and (3) investigations of companies, among other situations (U.S.Food and Drug Administration, 2010). The U.S.DOJ has prosecuted dozens of pharmaceutical companies over recent years and with the monetary values of these case settlements available to the public, this becomes an important area to gain quantitative information regarding noncompliance. As a result of settlements and convictions by the U.S.DOJ, the HHS OIG requires many companies to enter into a Corporate Integrity Agreement (Volkov, 2012). CIAs are contracts agreed upon, typically as a result of litigation, by the HHS OIG and the company in question to "prevent off-label marketing violations, anti-kickback and False Claims Act violations" (Volkov, 2012). Because CIAs are issued in the most egregious noncompliance settlements, using them for research data gives insight into major industry issues.

Within the CDER, there are 5 divisions developed to focus on specific aspects of the U.S.FDA regulations. Table 2 shows the different divisions of the CDER, along with the abbreviation that will be used going forward and the purpose of each division. By looking specifically at the purpose of each division, one is able to differentiate the types of noncompliance committed to attain a better understanding of the core behaviors used in the industry.

TABLE 2 – DIVISIONS OF THE CDER

Division of CDER	Abbreviation	Purpose
Office of Prescription Drug Promotion	OPDP	Monitors promotional activities of drug companies including marketing and advertising materials.
Office of Unapproved Drugs and Labeling Compliance	OUDLC	Controls the sale and use of unapproved drugs and ingredients.
Office of Manufacturing and Product Quality	OMPQ	Ensures cGMPs are used, all pharmaceutical products produced and imported to U.S. meet all quality control measures so they are safe and effective for consumption
Office of Compliance/ Immediate Office	OC/IO	Promotes CDER's overarching mission to "minimize consumer exposure to unsafe, ineffective, or poor quality drugs" (Bernstein, 2012).
Office of Scientific Investigation	OSI	Ensures compliance by scientific investigators with laws and regulations including good clinical and laboratory practices (Center for Drug Evaluation and Research, 2012).

MAJOR AREAS OF NONCOMPLIANCE

In the pharmaceutical industry, there are several areas where noncompliance is usually discovered. Noncompliance can be exposed through many avenues, such as facility inspections by regulatory agencies and lawsuits brought on by the private sector. The most egregious and prevalent areas of concern include (1) failure to file, or falsifying, reports on safety data, (2) not remaining in compliance with current Good Manufacturing Practices, or cGMPs, (3) off-label drug promotion, and (4) violations of the False Claims Act (U.S.Food and Drug Administration, 2012). It should also be mentioned that many of these compliance issues are interconnected, with most recent high-monetary settlements being handed down first for noncompliance of regulations which then results in violations of the False Claims Act. Of the 12 most recent major settlements found on the FDA website where the guilty party was a pharmaceutical company as a

whole, 10 were found in violation of the False Claims Act, with those violations stemming from noncompliance issues (U.S.Food and Drug Administration, 2012).

Safety

The act of falsely reporting or failing to report safety data to regulatory agencies and health care professionals has become increasingly evident in recent years. Of the 26 pharmaceutical settlements where over $100 million were awarded between January 2009 and May 2011, 8 settlements worth over $8.6 billion were directly related to drug safety issues (Giniat, 2011). More recently, there have been two landmark cases—GlaxoSmithKline and Merck—where criminal and civil fines in excess of $850 million have been handed down in direct relation to drug safety claims and reporting (Office of Public Affairs, 2012; U.S.Attorney District of MA, 2011).

While penalties have increased, they matter most only when the fines involved match or exceed the profits gained from the infraction (Braithwaite, 2013; Gagnon, 2013). Increasing penalties to that level is controversial and politically charged. Instead the FDA is using Corporate Integrity Agreements [CIAs] with teeth, such as requiring that companies "compensate its sales force based on the quality of service offered to doctors instead of sales volume," to allow the "company to recoup bonuses or company stock for up to three years from executives caught engaging in illegal behavior", to post all payments given to health care providers on their company website so it will become public record, and to exclude companies from Medicare and Medicaid for breach of the CIA, effectively reducing possible future revenues significantly (McCarthy, 2012; Zwick, 2012). Further, they are targeting individual executives with criminal penalties and career-ending bans from future involvement in Medicare and Medicaid (Pickett, 2011; Wechsler, 2012; Zwick, 2012).

Current Good Manufacturing Practice Violations

Current Good Manufacturing Practices, or cGMPs, are regulations put in place to control the way that medications on the open market have been produced (U.S.Food and Drug Administration, 2012). The FDA explains that "adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations" (Food and Drug Administration, 2009). To violate a cGMP regulation, a company may not keep their manufacturing equipment maintenance records up to date, have inadequate methods of testing samples, or have contamination issues with their products. Recently, there has been an increase in warning letters and untitled letters issued from the OMPQ. Figure 1 shows that the incidence of noncompliance resulting in warning letters has increased from 0 letters in 2003 to 16 letters in the first 10 months of 2012, peaking in 2011 with 19 letters issued.

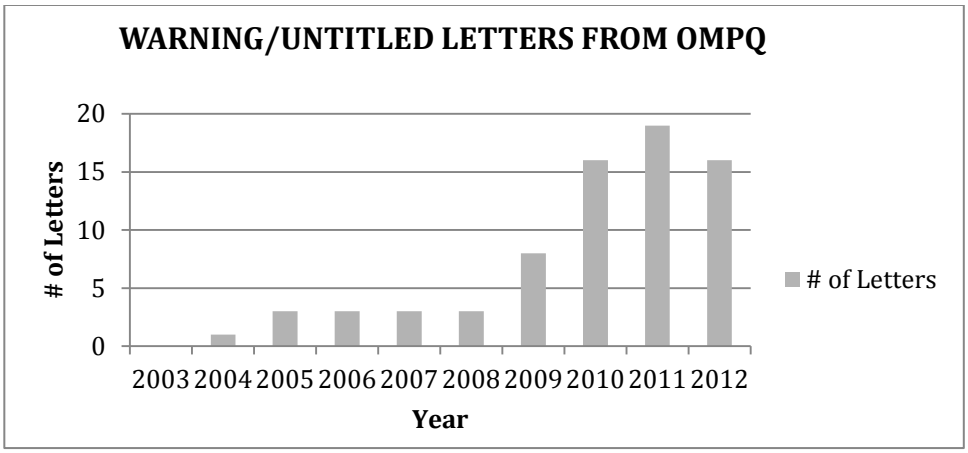

Figure 1—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012)

The issuance of warning and untitled letters is not the only indication that cGMP noncompliance is on the rise. As with drug safety violations, various cGMP issues are costing pharmaceutical companies millions of dollars in fines plus lost revenue for down-time at manufacturing facilities requiring necessary updates to return to compliance (Shanley, 2009). To avoid these fines, there is a growing trend of contract and generic drug manufacturing facilities in foreign countries, most notably China and India, which has become the focus of the OMPQ warning letters, as illustrated in Figure 2.

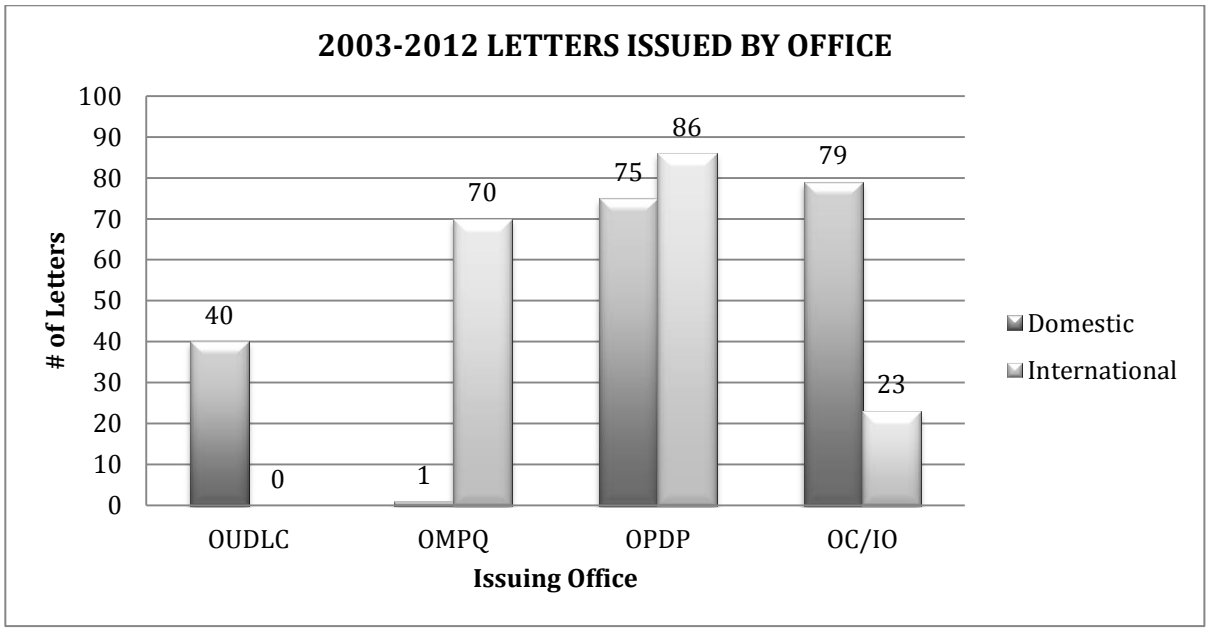

Figure 2—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012; Cacciotti & Clinton, 2011).

Off-label Illegal Promotion

Off-label promotion is characterized as the act of marketing a drug for uses that have not yet been approved by the Food and Drug Administration (Sampson & Wesoloski, 2012). It is a fairly common occurrence for medications to be prescribed by doctors for ailments that the FDA has not approved them for (Stafford, 2008). For instance, the medication Amitriptyline is approved to treat depression (Drugs.com, 2012). However, the drug is frequently prescribed for anything from irritable bowel syndrome to preventative therapy for migraines, despite the fact that there is little clinical research that has proven the effectiveness of that drug in treating those diseases. While doctors are allowed to prescribe a medication any way they see fit, pharmaceutical companies are strictly forbidden from marketing their drugs for any conditions not approved by the FDA (Stafford, 2008). Figure 3 shows the number of warning and untitled letters issued from the OPDP as compared to all other letters issued per year from all other divisions of the CDER in the last decade.

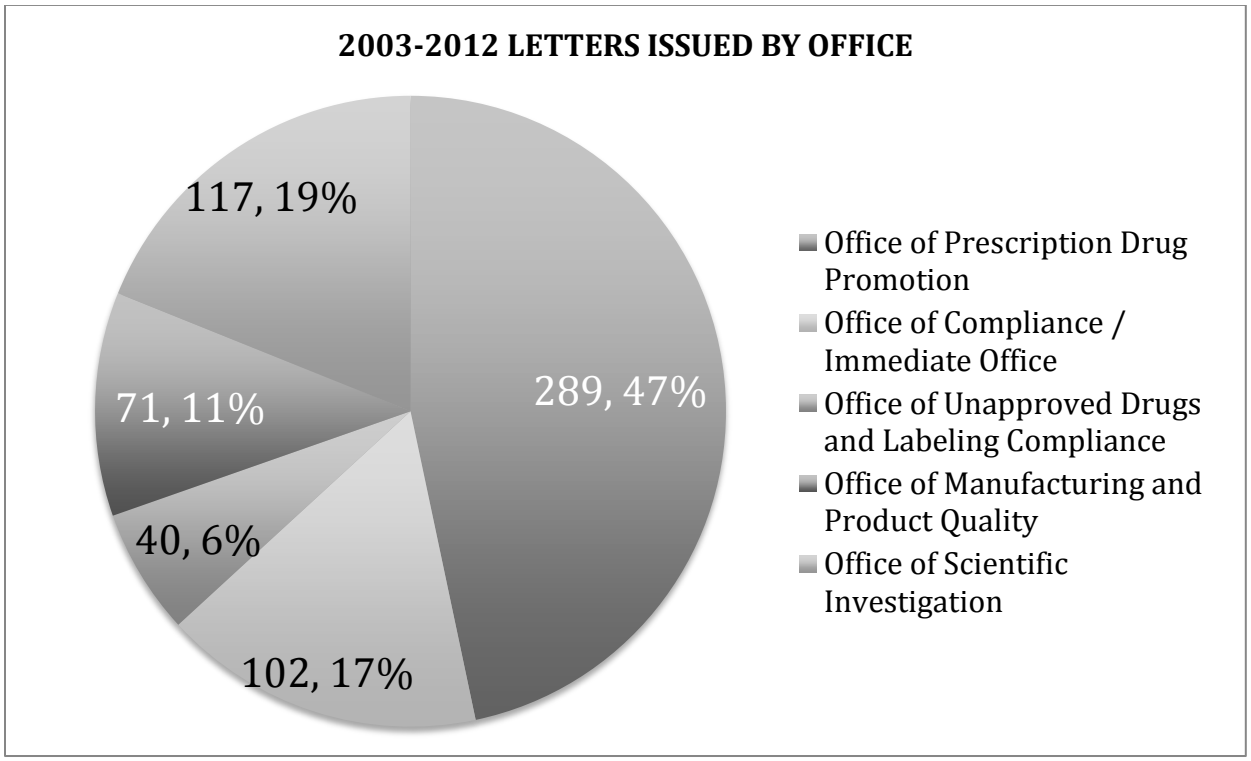

Figure 3—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012)

As is evident by the figure, the OPDP issued by far the largest proportion of letters at 47%, with a clear focus on drug marketing and advertising (U.S.Food and Drug Administration, 2012).

There are only a couple of years where the other offices issued significantly more letters, and there have been several years where the OPDP has issued more letters than all other offices combined (U.S.Food and Drug Administration, 2012). These practices can encompass many different points of noncompliance, from marketing a drug for a use while the drug is in the

approval phase to falsifying data to show other possible unapproved uses. These instances of off-label and illegal promotion show how interconnected noncompliance can be.

As complexity has grown, enforcement has become more difficult - the overall frequency of OPDP letters has declined (Senak, 2014), as illustrated in Figure 4.

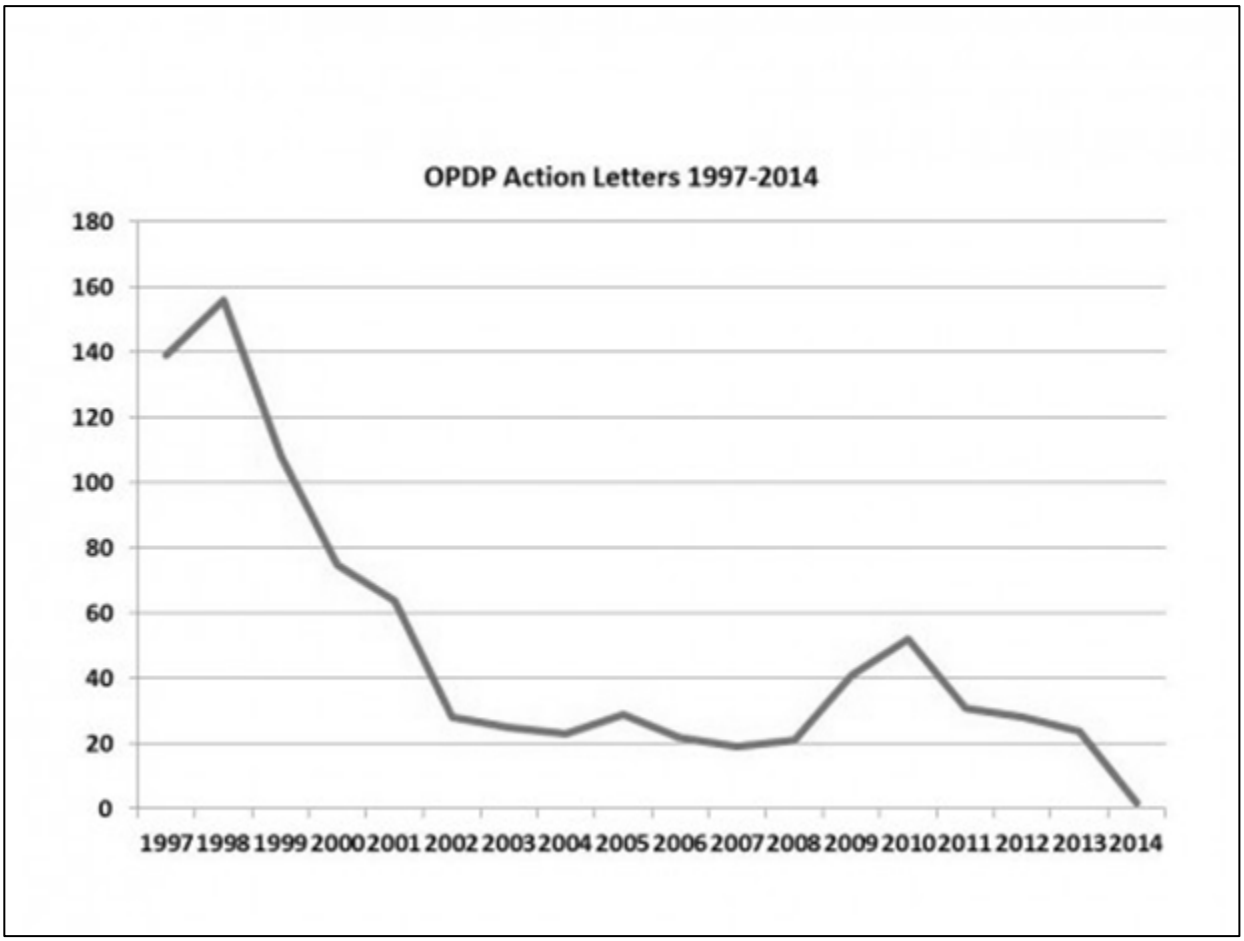

FIGURE 4—DATA COMPILED FROM THE U.S. FDA WEBSITE (U.S. FOOD AND DRUG ADMINISTRATION, 2012)

Government health program fraud

Several different points of noncompliance that could potentially defraud the government, and in turn violate the false claims act, include physician kickbacks, making false claims of using illegal promotional tactics that lead to increased sales, and reimbursement from federal and state programs, or price-reporting strategies. 83% of recent major investigations have resulted in civil fines and forfeitures for violating the false claims act. It should also be noted that, as figure 5 shows, 56% of fines and forfeitures collected due to pharmaceutical compliance investigations have been civil fines, which are paid based on the fraudulent activities occurring against government and state health programs (U.S. Food and Drug Administration, 2012). This can involve Medicare, Medicaid, Tricare, and any other health program paid for by taxpayer money (American Cancer Society, 2012). When civil fines are paid, the majority of the money goes to the federal government, with an additional portion being paid to state governments for their Medicaid programs (U.S. Food and Drug Administration, 2012). In the first half of 2012 alone, payouts of $5 billion and $1.6 billion had been made by pharmaceutical companies to federal and state governments, respectively (Almashat & Wolfe, 2012).

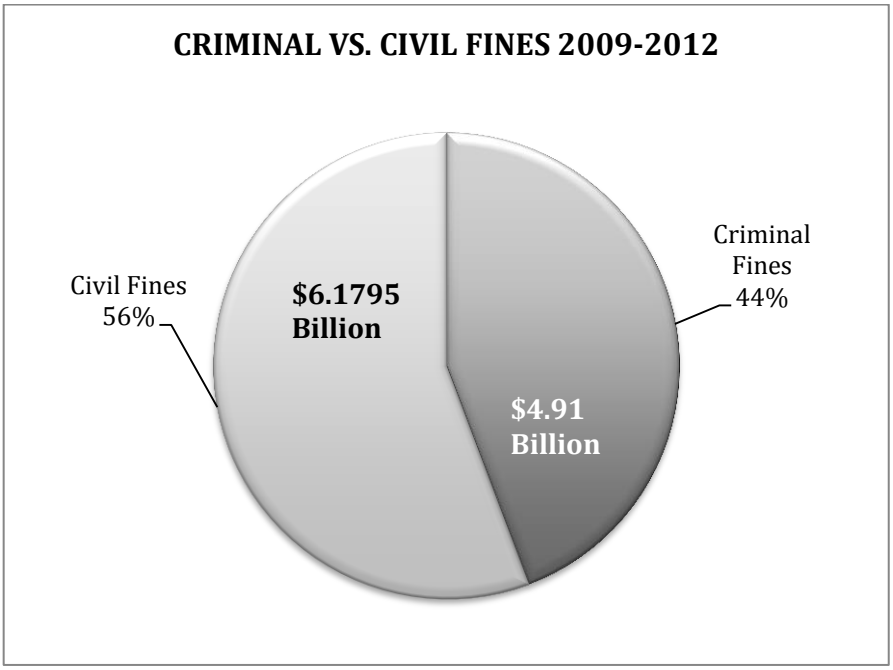

Figure 5—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012)

IMPLICATIONS

Pharmaceutical noncompliance has become an obvious issue over the last 15 years, and with the industry's transgressions of the mid-2000's still being played out in large investigations and court cases for years to come, there is seemingly no end in sight. In an age where heavy

regulatory control and oversight are increasingly necessary, there are thousands of pharmaceutical companies who find themselves in a noncompliant state on a seemingly daily basis. Warning letters are looked at in the industry very harshly because companies or people typically only receive them when there has been particularly egregious noncompliance (Gogtay et al., 2011). However, this is just the tip of the iceberg—the data being gathered is not comprehensive and some of the most important issues are not even being systematically tracked.

The contention that regulation is increasing is moderated by the record of enforcement. A breakdown of letters issued each year from 2003 to 2012 shows a clearer picture of how the CDER has taken action against noncompliance in recent years, as illustrated in Figure 6.

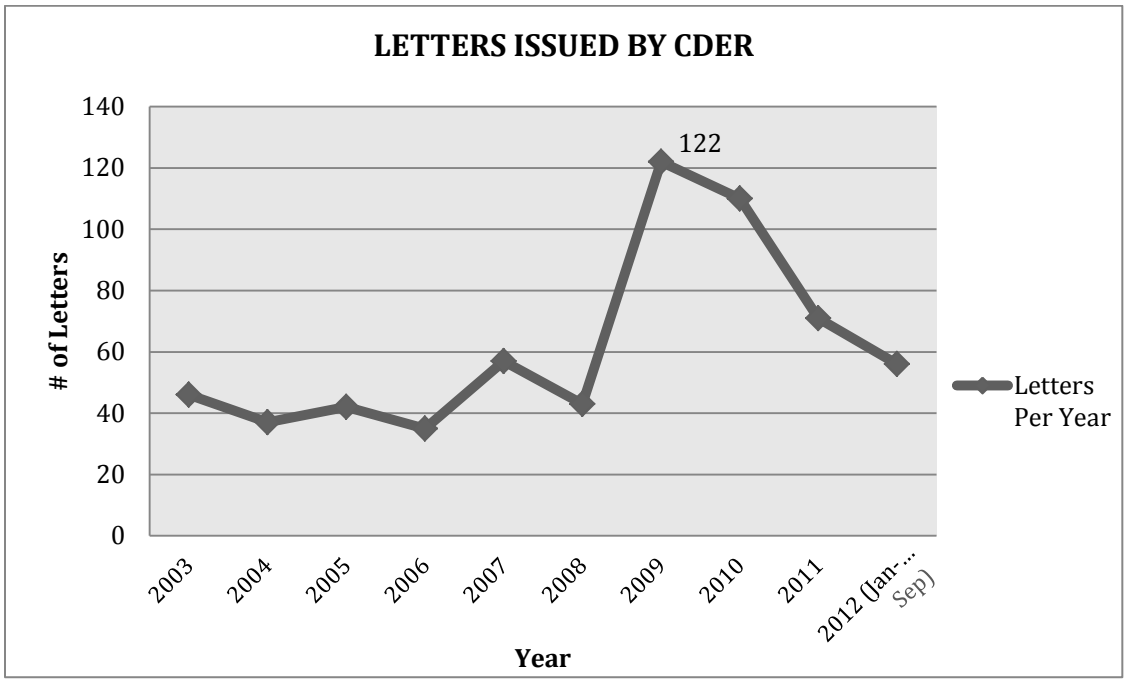

Figure 6—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012)

As can be seen in Figure 6, enforcement activities remained at similar levels for the first six years of the past decade before spiking to a high of 122 letters issued in 2009 (U.S.Food and Drug Administration, 2012). It should be noted that in 2009, 40 warning letters were issued by the OC/IO to many internet pharmaceutical retailers for misbranded or unapproved medications (U.S. Food and Drug Administration, 2012). Due to this apparent spike in warning letters, the year 2009 should not be considered consistent with average enforcement actions by the CDER or U.S.FDA. Looking at 2011 and the first 9 months of 2012, it appears the FDA has increased their direct oversight of the industry from the first 6 years of the past decade, with a 60% increase in warning and untitled letters issued in the past 22 months (U.S. Food and Drug Administration, 2012). However, the trend tracks downward. This increase in letters seems focused on areas of scandal: misleading off-label drug promotions and foreign drug manufacturing quality. The overall number of letters will shortly return to equilibrium, which is surprising given allegations of the increasing sophistication of the large drug makers in "gaming the system."

There are also serious resource constraints (Light, Lexchin & Darrow, 2013; Senak, 2011). For example, when analyzing regions impacted by the OPDP, the letters on drug promotion are dispersed evenly between U.S.and European countries, with a small percentage in Asia (U.S.Food and Drug Administration, 2012), as illustrated in Figure 7.

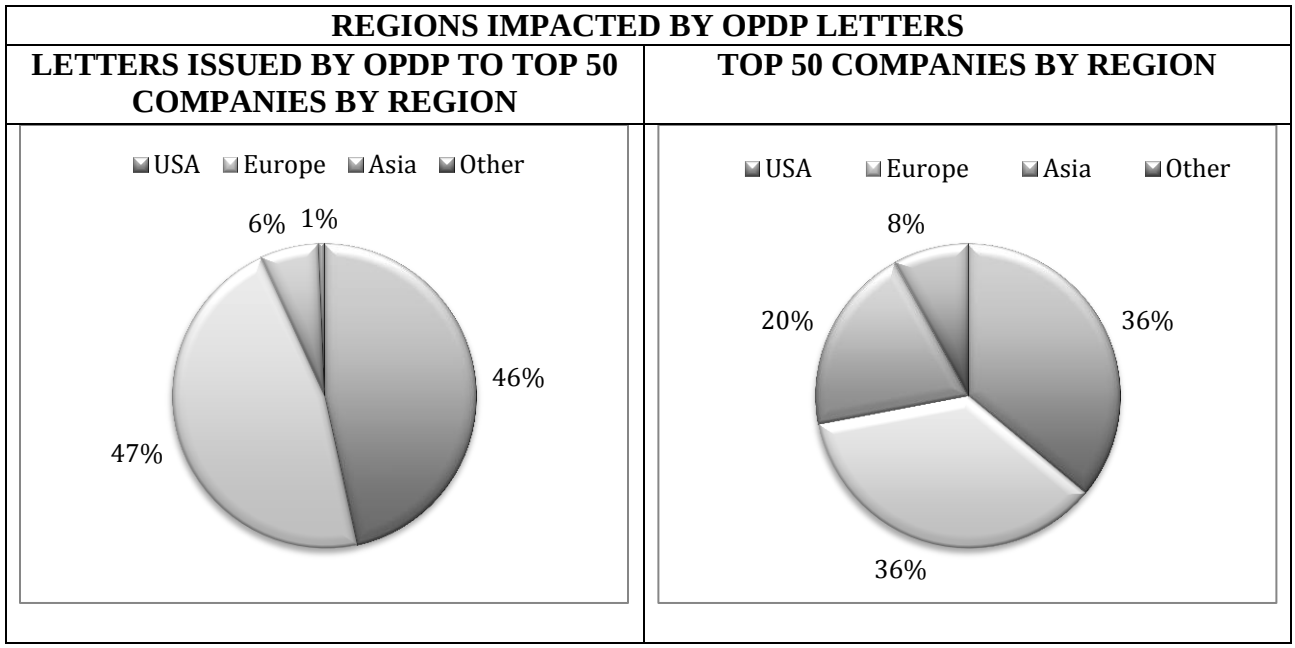

Figure 7—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012; Cacciotti & Clinton, 2011)

This focus on America and Europe, with the relative exclusion of Asia, is not an accurate reflection of emerging supply chain trends (Zwick, 2012). This seems to be driven more by appearances of enforcement parity between domestic and foreign drug makers in Europe, overlooking the explosion of Asian drug manufacturing, as constrained by political and resources issues. Critics summarize:

> The current Food and Drug Administration (FDA) system of regulating drug safety has serious limitations ... the public increasingly perceives the FDA as having become too close to the regulated pharmaceutical industry; the FDA's safety oversight structure is suboptimal; and the FDA's expertise and resources in drug safety and public health are limited. (Furberg et al. 2006)

Drug Promotion

Companies with more visibility, larger advertising budgets, and more marketing personnel have an increased susceptibility to being targeted for promotional noncompliance (Mintzes et al., 2013). This is to be expected following spectacular scandals such as Depakote, where Abbott maintained a dedicated sales force to market the drug to nursing homes when no evidence of efficacy for elderly patients existed, and evidence of adverse side-effects was being suppressed

(Office of Public Affairs, 2012). In the future, the FDA has announced an expansion of the scope of its investigations to include the internet and marketing on social networking sites (Zwick, 2012). This is one arena where metrics are relatively clear-cut –a comparison of promotional claims versus effective, approved FDA uses.

Safety

With metrics, the adage is "garbage in, garbage out." Beyond minimizing political influence in data analysis and interpretation, the FDA must be given the authority and resources necessary to gather comprehensive, accurate data. Critics allege the FDA lacks the capacity to track and enforce drug safety issues (Light, Lexchin & Darrow, 2013; Zwick, 2012) such as:

> ... the design of initial preapproval studies lets uncommon, serious adverse events go undetected; massive underreporting of adverse events to the FDA, post marketing surveillance system reduces the ability to quantify risk accurately; manufacturers do not fulfill the majority of their post marketing safety study commitments; the FDA lacks authority to pursue sponsors who violate regulations and ignore post marketing safety study commitments ...'' (Furberg et al., 2006)

Manufacturing Quality

Given the growing number of firms not remaining in compliance with current Good Manufacturing Practices, or cGMPs, this is an area of particular concern. The FDA response of doubling the frequency of drug company inspections is only as effective as the expertise of FDA examiners (Furberg et al., 2006; Hale, Borys & Adams, 2011). The FDA is trying to pay particular attention to focus on the quality of the supply chain, so 30 percent of drug maker inspections now are taking place outside the United States. (Zwick, 2012). While the industry has evolved from single corporations to complex, inter-dependent supply chains, the FDA analysis lags behind.

CONCLUSION

The FDA seems reactive, focusing on areas brought to the forefront by crises and scandal. In this arena, policy makers seem to adopt a "remedial," or problem-oriented, approach towards drug safety enforcement. They are criticized for ambiguity in their standards of how to balance public health with profit motive. This is true of most public policy:

> The characteristics of the strategy support and encourage the analyst to identify situations or ills from which to move away rather than goals toward which to move. Even short term goals are defined largely in terms of reducing some observed ill rather than in terms of a known objective of another sort. Policy aims at suppressing vice even though virtue

> cannot be defined, let alone concretized as a goal; at attending to mental illness even though we are not sure what attitudes and behaviors are most healthy; ... at eliminating inequities in the tax structure even though we do not agree on equity; [etc.]... (Braybrooke & Lindbloom, 1963, p. 102)

Their attempts to remediate are usually so cumbersome they prove to be as controversial as the set of problems they were intended to remedy. Concerning regulation and policy, consensus evaporates as specific rules emerge. As the adage notes: "the Devil's in the details."

This is due, in no small part, to the plethora of unfunded mandates hoisted upon the FDA by Congress. They are being asked to do more with less, but that is proving very difficult. Right now FDA oversight consists of inspections, warning letters, fines, CIAs, sanctions on executives and the nuclear option—banishment from government health care program markets (Office of Inspector General, 2012; Senak, 2011; U.S.Food and Drug Administration, 2010; Volkov, 2012). However, the FDA's ability to deploy and enforce is chronically undermined by political interference and resource constraints.

In the private sector, businesses have responded to similar dynamics with customer profiling—providing different types of customers with different levels of services, given a cost/benefit analysis (Whittle & Foster, 1989). For FDA regulation purposes, the following variables can be used to profile drug manufacturers:

The Supply Chain as the Level of Analysis

Tracking individual firms tends to undermine the proposition that large pharmaceutical firms deserve more oversight. Note that the proportion of letters given to larger firms is hardly disproportionate, as illustrated in Figure 8.

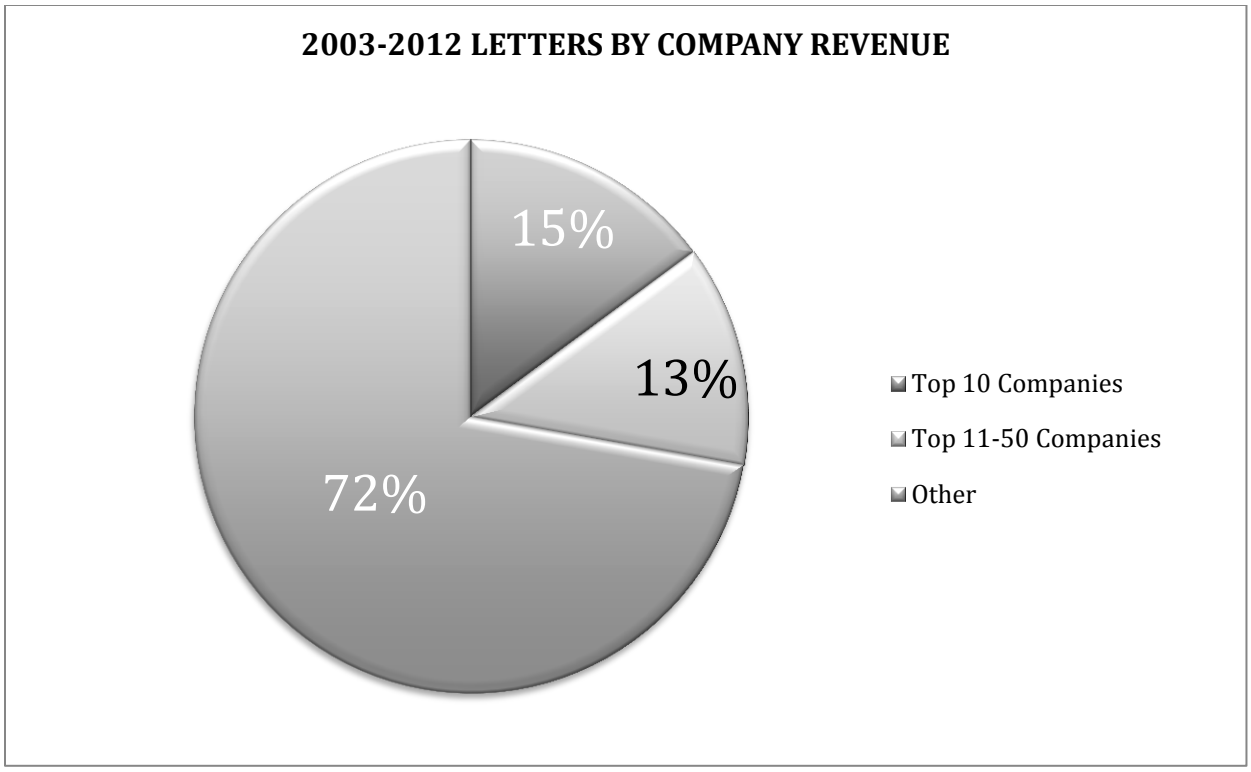

Figure 8—Data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012; Cacciotti & Clinton, 2011)

However, these large firms may be offloading violations further up and down the supply chain. Considering the non-compliance rates by an entire supply chain gives a more accurate picture, but is not being tracked.

The sophistication of the supply chain

The more sophisticated the supply chain, the tighter the regulatory oversight should be. Size, resources, and dedicated marketing departments increase the likelihood of non-compliance in favor of market penetration and expansion. Smaller, less sophisticated supply chains lack the resources and the capacity to "game the system," and are much more likely to do everything they can to avoid the ire of the FDA—they are not "too big to fail."

The profit potential of non-compliance

FDA penalties are a credible threat for smaller supply chains, whose profitability would be devastated by FDA action. However, as the potential profitability of non-compliance increases, so should regulatory oversight. These relationships are illustrated in Figure 9.

DRUG MAKER ENFORCEMENT PROFILES

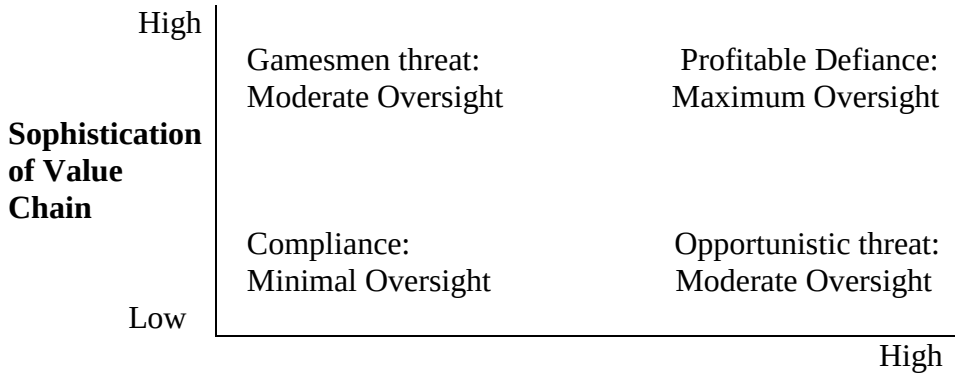

Figure 9—Profit Potential of Non-compliance

Minimum oversight.

When drug makers are medium or smaller, and are embedded in medium to small supply chains, they tend to be extremely compliant, and should be rewarded for their performance. Streamlining procedures and minimizing oversight seems more than appropriate. The DOJ and HHS OIG have already adopted this policy, as illustrated in Table 3.

TABLE 3 – DATA TYPES BY AGENCY

Agency	Data	Benefits	Disadvantages
U.S. Food and Drug Administration (U.S.FDA), Center for Drug Evaluation and Research (CDER)	Inspectional Observation (483), Warning Letter, Untitled Letter	Target Specific Violations, quantitative and qualitative data	Only covers noncompliance observed
U.S. Department of Justice (U.S.DOJ)	Criminal and Civil Litigation and Settlements	Quantifies noncompliance by monetary value	Does not always reflect noncompliance in smaller companies
U.S. Department of Health and Human Services, Office of Inspector General (HHS OIG)	Corporate Integrity Agreement (CIA)	Issued to companies based on noncompliance	Not typically issued to smaller companies or outside of litigation/settlements

Moderate oversight

When firms are tempted to be non-compliant by the sophistication of their supply chains and marketing departments, or by the opportunity to "make a killing"—in both profits and patients—they deserve a higher level of oversight. This oversight can diminish if these firms are willing to agree to CIAs with penalties for non-compliance drastic enough to offset those temptations, or given a superior history of past compliance (no scandals).

Maximum oversight

When firms have little reason not to defy regulation, given the sophistication of their marketing and their ability to offload risk upstream or downstream in their supply chains, there is no reason not to focus most available enforcement resources here. Given the political pull of "Big Pharma" this is unlikely to happen.

Potential future research methods to continue on this path may include detailed tracking the response of companies to the penalties they have incurred by the FDA and civil agreements and settlements. Have companies swept their settlements under the rug, to remain out of sight or have they approached them head on, making critical process changes that will ensure a much lessened likelihood of them ever happening again? How companies respond to the negative reactions of public and private entities alike may project the future trajectory of noncompliance in the pharmaceutical industry.

Such performance indicators need to be systematically tracked. It can be observed at times that current oversight practices do not follow any specific decision trees or algorithm to ensure qualified decisions are provided as options. Given this current state, there exists an opportunity for FDA Inspectors to gather and assess key performance indicators (KPIs) from drug makers for use in a Decision Support System (DSS), based upon daily electronic data interchange existing today between drug companies and the FDA. A DSS is a computer-based information system that supports business or organizational decision-making activities by shifting through and organizing vast amounts of data for analysis (Wainright & Mulligan, 2013). While various DSS systems are commonly employed by pharmaceutical companies in a variety of functions such as R&D and supply chain management for decades (Iseli et. al., 1991; Weber & Ellram, 1993), government agencies continue to seriously lag in their adoption (Staab & Studer, 2010).

Such a system would guide FDA Inspectors on the level of monitoring required by the DSS and then necessitate at what level of detail (and how often) on-site inspections should occur based underperforming KPIs, relative to the DSS set algorithms. Benefits include:

- ***Transparency:*** The KPI reporting mechanism will allow drug companies to provide accurate and full disclosure on a weekly or monthly basis regarding cases that are medically and scientifically reviewed.
- ***Costs savings***: The potential for significant labor savings exists for FDA Inspectors, given that lengthy onsite inspections would be limited to only when necessary (based upon KPIs decision models). Given the expected drop in resource demand for pharma inspection, FDA inspector resources could be deployed to other departments in need.

- ***New Best Practices:*** New best practices for monitoring and controlling drug companies can be established, based on observations made regarding supply chain size and complexity.

If implemented, FDA inspectors would benefit from a self-reporting system utilized by drug makers, which would require minimal resource support from the FDA over the long-term. This decision support model would provide a single inspector with a wide purview on compliance performance for variously sized drug makers with the "click of a mouse" versus the lengthy onsite hands-on approach during a routine site visit.

For example, examine a hypothetical dashboard ("report card") and reporting mechanism for use by the FDA Pharmaceutical Inspectors to measure and determine the level of future oversight required for a drug manufacturing company, based upon a specific set of metrics, as illustrated in Figure 10:

COMPLIANCE DASHBOARD

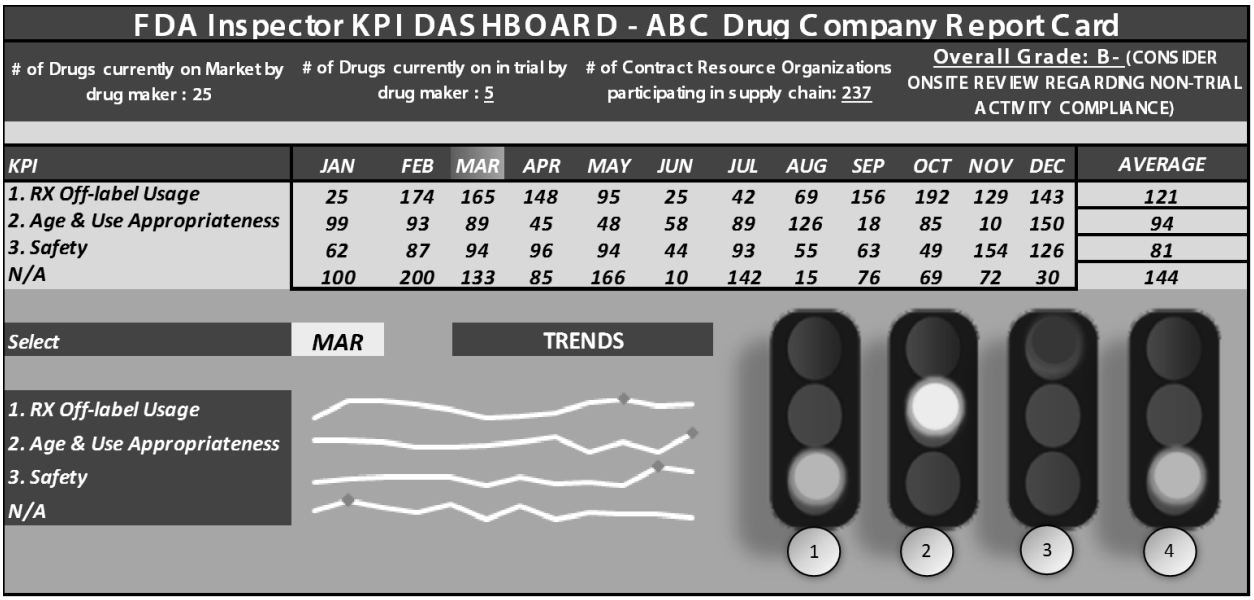

Figure 10

Drug Promotion

- RX Off-label Usage - develop KPI per drug classes, and the likelihood of off-label usage algorithm)
- Age & Use Appropriateness (KPI based on trials and source of usage)

Safety

- Adverse Event (for both off label and as directed usage) (KPI per drug, based upon relative % to RXs)
- # of Drugs currently on Market by drug maker (per defined threshold matrix associated to this value)

- # of Drugs currently on in trial by drug maker (per defined threshold matrix associated to this value)
- # Contract Resource Organizations (CROs) participating in supply chain (per defined threshold matrix associated to this value)

Given the politics and costs involved, the likelihood of such a system remains problematic. The subject of noncompliance is something that both pharmaceutical companies and their regulatory bodies will have to grapple with perpetually, for as long as it continues to be so financially enticing. Take solace in the fact that the vast majority of pharmaceutical companies continue to comply with regulations and provide the very best treatments they have to offer, with a conscious eye on healing, rather than hurting.

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