

Strategic defiance and profitability in the pharmaceutical industry

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ABSTRACT

The issue of pharmaceutical non-compliance has become a popular topic in recent years, given the increasing public scrutiny of a growing list of dangerous drugs, released despite U.S. Food and Drug Administration (FDA) safety regulations. This paper explores the tensions and tradeoffs between regulatory compliance versus defiance in the pharmaceutical industry. In particular, FDA countermeasures designed to undermine the potential profitability of unsafe pharmaceuticals are evaluated and implications are discussed.

Keywords: Pharmaceutical industry, compliance and non-compliance in pharmaceuticals, FDA regulations, strategic defiance and profitability

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INTRODUCTION

The year 2009 was a banner year for non-compliance. After a series of drug scandals, warning letters increased to 122 letters issued in 2009 (U.S. Food and Drug Administration, 2012, November 29). One stream of research suggested that large firms had realized that regulatory defiance was fiscally justifiable - warning letters become an expected expense (Braithwaite, 2013; Brezis & Wiist, 2011; Gagnon, 2013; McCarthy, 2012). From this perspective, unless compliance becomes cost-effective, regulations possess consistent clarity, and penalties outweigh the profits gained from non-compliance, the larger the firm, the greater the non-compliance (Mansfield, 2005). The FDA has devised a new enforcement strategy they claim will provide enough deterrence to undermine the profitability proposition associated with strategic defiance. This paper systematically assesses the scope of regulatory defiance and the adequacy of the FDA countermeasures.

THE PHARMACEUTICAL INDUSTRY

As of January 20, 2015, the pharmaceutical market can be summarized as follows (SelectUSA, 2015, 1; Acquisdata, 2015, January 20):

“The United States is the world’s largest market for pharmaceuticals and the world leader in biopharmaceutical research. U.S. firms conduct 80 percent of the world’s research and development in biotechnology and hold the intellectual property rights to most new medicines. In 2010, the pharmaceutical sector employed approximately 272,000 people, and according to the Pharmaceutical Research and Manufacturers of America (PhRMA), those manufacturers spent \$67.4 billion on research and development in 2010.”

Biologics, over-the-counter (OTC) medicines, and generics show the most promise for growth and are increasingly competitive. Biologics, a \$67 billion market in 2010, accounted for a quarter of all new drugs in clinical trials or awaiting Food and Drug Administration approval. The OTC market will grow and is driven by a growing aging population, consumer trend to self-medication, and the conversion of drugs from prescription to OTC status. U.S. generic drug sales were valued at \$78 billion in 2010. (SelectUSA, 2015)

The world’s largest free-pricing market for pharmaceuticals is the U.S. market, with a favorable patent and regulatory environment. Product quality, safety and efficacy, and price typically determine successful product competition. The U.S. market is the preferred home for growth in the pharmaceutical industry due to the U.S. government’s support of biomedical research, unparalleled scientific research, and innovation. (SelectUSA, 2015)

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). This market is oligopolistic, with three companies, Cardinal Health, McKesson, and AmerisourceBergen, grossing \$290 billion of that revenue, or 85% (Fein, 2012). 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 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, a cost of \$4 to \$11 billion per drug may be more accurate (Harper, 2012).

The U.S. Food and Drug Administration (FDA) asserts that regulations are necessary to ensure that the products 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 the 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, Lexchin, Sutherland, Beaulieu, Wilkes, Durrieu, & Reynolds, 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 (Borowski, Mikhli, & Pham, 2007; Lowe, 2011).

Critics attack such regulation as prohibitively costly and often unnecessary (Hale, et al., 2011). While the industry does not entirely disagree with government regulations, they question the scale and scope. Regulations may have become too extensive and intrusive, particularly on the discovery of new therapies. “In 1996, the FDA approved 53 new drugs, but by 2010 the number of new drug approvals had shrunk more than 50 percent to only 21” (Fikes, 2011, 1). The industry believes that the increasingly difficult requirements for safety also are cutting into the ability to produce new medications. “Drugs are not more dangerous, it is just that many expect a 'risk-free' drug,” he said. “There is no such thing. The FDA should instead be weighing the benefit to the patient when evaluating these drugs” (Fikes, 2011, 1; Merritt & Goldsmith, 2014). The industry also has complaints regarding the pace at which reviews take place and the speed at which industry fees are increasing (Fikes, 2011).

Of particular concern is the necessity for each new product being brought to market to be so superior to existing therapies, termed, “Better than The Beatles Syndrome” (Ledford, 2011). With many very effective drugs already on the market, increases in generic-drug offerings, and an expectation that any new drug for approval must be highly superior to current offerings, many companies in the industry do not see the value of researching certain diseases. Further, this degree of intrusiveness creates a business case for non-compliance (Hale, et al., 2011).

NON-COMPLIANCE METHODOLOGY

In an age where heavy regulatory control and oversight are most commonly found, there are thousands of pharmaceutical companies who find themselves in a non-compliant state on a regular 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 non-compliance (Gogtay, Doshi, Kannan, & Thatte, 2011; Goodwin & Jacobs, 2013). Also, warning letters and other regulatory actions can have some serious operational and financial impacts (Asotra, Cossin, & Yacobi, 2012):

- The company loses its credit line and must pay upfront for purchases of materials and equipment.
- Current R&D programs and developmental work are directly impacted due to a diminished level of financial support.
- R&D resources are shifted and devoted to address production and scaled-up manufacturing issues and, thus, extensive as well as expensive key R&D resources are used to address routine operational and commercial manufacturing tasks.
- It may create a reduction of R&D force and investment due to lack of adequate funds to support current work.
- It may lead to a loss of customers.
- It increases the cost of production and loss of competitiveness that directly affects sales levels.
- The company may lose opportunities for joint venture partners and programs.
- It may lead to poor company morale.
- Dissatisfied customers and supply chain members increase with resultant loss of business, sales, reputation, credibility, and trust.
- Increased government scrutiny.

In an effort to quantify the incidence of non-compliance and the implications that non-compliant behavior poses to the industry, Table 1 (Appendix) shows the different agencies and the benefits and disadvantages of the data they gather to quantify non-compliance.

The U.S. FDA CDER (Center for Drug Evaluation and Research) issues Warning Letters, Untitled Letters, and Inspectional Observations 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 (Department of Justice) 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 non-compliance. As a result of settlements and convictions by the U.S. DOJ, the HHS OIG (U.S. Department of Health and Human Services, Office of Inspector General) requires many companies to enter into a Corporate Integrity Agreement (CIA) (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-kickbacks, and False Claims Act violations (Volkov, 2012; Edgeworth, Ford, Helman, Singleton, & Yarin, 2009). Because CIAs are issued in the most egregious non-compliance settlements, using them for research data gives insight into the major issues in the industry.

Within the CDER, there are five divisions developed to focus on specific aspects of the U.S. FDA regulations. Table 2 (Appendix) 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 non-compliance committed to attain a better understanding of the core behaviors used in the industry.

Additionally, advertising for pharmaceutical products also is regulated by the FDA. In general, advertising and promotion in the pharmaceutical industry take two forms: direct advertising to physicians (DTP) and DTCA (Direct to Consumer Advertising). There is a substantial history of regulatory policy and guidelines with respect to DTCA. For example, the 1962 Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act gave the FDA

its current responsibility for monitoring pharmaceutical drug promotional materials and established policies for marketing efforts including (Kalyanara & Phelan, 2013):

- Pharmaceutical promotional materials cannot be false or misleading.
- The advertising must provide a “fair-balance” coverage of the risks and benefits of using the drug.
- The company must provide a summary of contraindications, side effects, and effectiveness.
- The ads also must meet specific guidelines for readability and size of print.

As advanced both by medical insurers and pharmaceutical firms, Kalyanara & Phelan (2013) have provided support to the premise that direct advertising to the consumers (DTCA) has the effect of the consumers seeking that advertised brand of drug, while also expanding the drug category. In addition, it is interesting to note that the effect of DTCA was strengthened by the Food and Drug Administration’s clarification of rules governing broadcast advertising in 1997 and 1999 (Dave & Saffer, 2012).

However, it should be understood that while these DTCA effects are significant and substantial, they are less than the effects of price and direct advertising to physicians (DTP). Therefore, price and DTP are better instruments for firms to use to increase market share and primary demand, this assumes that the costs of implementation of all the instruments (DTCA, DTP, and price discounts) are similar. The authors also generalized that later entrants typically achieve a lesser share than the pioneering brand if they enter the market with a parity product and parity marketing efforts. (Kalyanara & Phelan, 2013)

RATIONALE FOR NON-COMPLIANCE

Regulatory non-compliance stems from: (1) compliance being too costly, (2) regulatory ambiguity, and (3) risk-based assessment leading to regulatory defiance. Motives for non-compliance are rarely mutually exclusive, with many variables entering the equation. Many of these compliance issues are interconnected, with most recent high-monetary settlements being handed down first for non-compliance of regulations, and subsequently for violations of the False Claims Act.

Compliance Costs

One of the most frequently used reasons for pharmaceutical non-compliance is that it is too costly to the company (Hale, et al., 2011). Figures based on annual reports assume that the cost of compliance in a company is about 30% of the combined total from cost of sales and R&D spending (Malhorta, 2012; Bruttin & Dean, 2004). For a medium-to-large sized manufacturing company, that is equal to approximately €40 million, or \$53 million at that time (Bruttin & Dean, 2004). Such firms are forced to either focus their efforts on a reduced product range or curtail compliance with regulations they perceive as being routinely overlooked or unenforced by the FDA.

Safety

The act of falsely reporting or failing to report safety data to regulatory agencies and health care professionals to cut costs has become increasingly evident in recent years. Of the 26

pharmaceutical settlements where over \$100 million was awarded between January 2009 and May 2011, eight settlements worth over \$8.6 billion were directly related to drug safety issues (Giniat, 2011).

More recently, there have been two landmark cases 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, May 7 & July 2). In each case, non-compliance occurred, but what varies is the way in which GlaxoSmithKline (GSK) and Merck were out of compliance with safety regulations. (U.S. Attorney District of MA, 2011) Avandia was a blockbuster diabetes medication for GlaxoSmithKline, with sales peaking at \$2.5 billion in the U.S. in 2006 (McGuire, 2007). It was available as a stand-alone medication or also in combination with popular diabetes medications Metformin (Avandamet) and Glimperiride (Avandaryl). However, the drug quickly became linked to major cardiovascular problems, including heart attack and stroke (Freeman, 2010). It was found in July of 2012 by the U.S. FDA Office of Criminal Investigations that "...between 2001 and 2007, GSK failed to include certain safety data about Avandia, a diabetes drug, in reports to the FDA that are meant to allow the FDA to determine if a drug continues to be safe for its approved indications and to spot drug safety trends" (Office of Public Affairs, 2012, July 2, 1). More specifically, safety data from post-market surveillance activities, or long-term studies conducted after the drug was on the market, was withheld from the FDA (Office of Public Affairs, 2012, July 2). To clarify matters, initial clinical trials were done on this medication, and the FDA did approve this drug to be safe and effective based on the data provided during the approval process (Office of Public Affairs, 2012, July 2). However, typically, Phase III clinical trials do not last long enough to truly understand long-term effects of a medication (Chicago Research Center, Inc., 2008). Therefore, pharmaceutical companies have an obligation to run post-market surveillance on approved medications and provide necessary safety data from the post-market studies so the drug may remain on the market. The FDA believed that GlaxoSmithKline was out of compliance with the regulations governing the act of providing the FDA with all applicable safety data from post-market studies. "GSK has agreed to plead guilty to failing to report data to the FDA and has agreed to pay a criminal fine in the amount of [\$242.6 million] for its unlawful conduct concerning Avandia" (Office of Public Affairs, 2012, July 2, 1; Mingrone, Panunzi, De Gaetano, Guidone, Iaconelli, Leccesi, Nanni, Pomp, Castagneto, Ghirlanda, & Rubino, 2012; Sapkale, & Pradhan, 2012; GlaxoSmithKline PLC., 2012; Merck & Co., Inc., 2012).

Regulatory Ambiguity

Another point of contention between the industry and regulatory agencies involves the relative ambiguity of some regulations and classification systems (Benet & Larregieu, 2010). One recent example of this perceived ambiguity involves 14 warning letters sent to various pharmaceutical companies in 2009 regarding search ads used on Internet search engines (Clifford, 2009). The FDA's reasoning for sending these letters was that the ads did not contain any risk information about the drugs advertised (Clifford, 2009). The industry believed that the 95 characters allowed for these ads was not sufficient to convey the risk profile of the medication, and argued that trying to explain risk in such a short ad would cause even more confusion for the consumer (Clifford, 2009). There was also an understanding by the industry of the so-called "one-click rule," where "as long as pharmaceutical companies provided risk information within one click of their search ads - on the page that the ad linked to - they assumed

they were in compliance” (Clifford, 2009, 1). The FDA has not issued any clear guidelines on this matter to date. So, the company needs to be proactive and address their consumers directly.

The industry has asked for clarity of the Code of Federal Regulations (CFR) for areas such as electronic data in recent years, but to no avail (Taylor, 2011). The FDA’s silence “has led to a ‘gotcha’ mentality that uses enforcement, rather than guidance, to communicate policy” (Shaffer, 2012, 1). This has caused a considerable amount of resentment from the industry toward the FDA and has even lead to a citizen petition having been filed by seven major pharmaceutical companies with the FDA looking for guidelines on off-label promotion information regarding “manufacturer responses to unsolicited requests, scientific exchange, interactions with formulary committees, payers and similar entities, and dissemination of third-party clinical practice guidelines” (Fuerst & Ittleman, PL, 2011, 1).

Inconsistency in enforcement of non-compliance also has frustrated the industry. Due to lack of clarity with regulations and guidance, when a company or group of companies operates in a certain way consistently without enforcement actions taken against them, there is an assumption of compliance. However, this assumption can be arbitrarily challenged. In October of 2012, for example, the FDA issued a warning letter to the Burzynski Research Institute, Inc. and the Burzynski Clinic regarding promotional claims they made about products currently in testing. These claims proved to be virtually identical to claims made by many other companies in the industry (Shaffer, 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, September 7). 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, June 25, 1). Violating cGMPs to cut costs is the result of regulations being perceived as either too ambiguous or unnecessarily intrusive. 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 (Office of Manufacturing and Product Quality). Figure 1 (Appendix) shows that the incidence of non-compliance has increased from zero letters in 2003 to 16 letters in the first 10 months of 2012, peaking in 2011 with 19 letters issued.

The issuance of warning and untitled letters is not the only indication given in recent years that cGMP non-compliance is on the rise. As with drug safety violations, various cGMP issues are costing pharmaceutical companies and even specific people within a company millions of dollars in fines and possibly even more money in lost revenue for down-time at manufacturing facilities requiring necessary updates to return to compliance (Shanley, 2009). Table 3 (Appendix) showcases some major cGMP cases in 2009, including enforcement actions taken by the FDA. For example, in the fall of 2010, SB Pharmco Puerto Rico, Inc., a subsidiary of GlaxoSmithKline, agreed to pay a total of \$750 million in criminal and civil settlements related to manufacturing violations (U.S. Attorney's Office, District of MA, 2010). Various issues arose between 2001 and 2005 regarding several different products, including a failure to ensure that Kytril and Bactroban were free of contaminants, and an ineffective process that resulted in

controlled-release Paxil tablets breaking in half (U.S. Attorney's Office, District of MA, 2010). This manufacturing facility had previously been issued a warning letter in 2002, citing several violations including a failure to recall contaminated products before being forced by the FDA, failure to ensure batch uniformity, and a complete lack of due diligence of the quality control unit as a whole (U.S. Food and Drug Administration, 2002).

In response to quality diminishment, Orloff (2014) has suggested that reducing variation to improve quality would lead to minimized costs and maximized profits while reducing risk to the patient. Orloff (2014, 3) contends that the “key to a ‘maximally efficient, agile, and flexible industry’; could be a single meaningful metric to focus attention on process variation and separate regulatory oversight into distinct departments for compliance and performance. This metric is the out-of-specification (OOS) rate.”

Risk-Based Analysis

Following the billions of dollars spent on fines and forfeitures due to non-compliance within the industry, the total cost of compliance within any pharmaceutical company has increased to the point that most companies in the industry have dedicated compliance departments (Medical News Today, 2009).

However the current costs of non-compliance may be ineffective from a cost/benefit perspective (Braithwaite, 2013; Gagnon, 2013; McCarthy, 2012). For example, estimating the costs of compliance using the 30% of the combined total from cost of sales and R&D spending formula (Malhorta, 2012), in 2011 Pfizer, with \$15.1 billion attributed to cost of sales and \$9.1 billion on R&D expenses, estimated costs of compliance at \$7.26 billion (Pfizer, Inc., 2011). Note this figure is more than 3 times the \$2.3 billion amount Pfizer paid to plaintiffs, federal, and state governments in 2009 for major infringements (Pelofsky & Pierson, 2009). Even considering the legal costs on top of the settlement reached, it appears that the cost of total compliance was far greater than the litigation costs. For example, in 2002, 94% of Pfizer’s \$2.27 billion in sales of the anti-seizure Neurontin came from off-label indications, such as bipolar disorder and neuropathy. While the FDA prohibits off-label sales, billions of dollars in revenue may justify their defiance from a purely financial perspective (Hale, et al., 2011; McCarthy, 2012). This suggests that even a comprehensive risk analysis may recommend strategic disregard for certain regulations.

Off-Label of 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 (Brezis & Wiist, 2011; 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. Doctors are allowed to prescribe a medication any way they see fit, but pharmaceutical companies are strictly forbidden from marketing their drugs to treat anything but the FDA-approved uses (Stafford, 2008). When analyzing data specified in the research methods section, the instance of marketing non-compliance is staggering. (Kesselheim, Mello, & Studdert, 2011)

For example, Figure 2 (Appendix) shows the number of warning and untitled letters issued from the OPDP as compared to all other letters issued from all other divisions of the CDER, a pattern which has been relatively consistent over the past decade. As is evident by Figure 2 (Appendix), the OPDP issued by far the largest proportion of letters at 47%, and this office oversees the marketing and advertising of medications (U.S. Food and Drug Administration, 2012).

As Figure 2 (Appendix) shows, 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. Also, of the 17 most recent large criminal and civil investigations conducted by the FDA, 12 have been fined specifically for off-label promotion (U.S. Food and Drug Administration, 2012, November 29). There are many companies to have been linked to off-label promotional practices, including Johnson & Johnson, Pfizer, Merck, Abbott Labs, and GlaxoSmithKline (U.S. Food and Drug Administration, 2012, November 29). These practices can encompass many different points of non-compliance, 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 non-compliance can be.

One of the largest cases regarding off-label promotion involves GlaxoSmithKline, and the overall case covered several medications that the company promotes (Office of Public Affairs, 2012, July 2). In the case of Paxil, the blockbuster anti-depression medication, the government alleges that for about five years, GSK was marketing the drug to patients under the age of 18, without the approval from the FDA for pediatric use (Office of Public Affairs, 2012, July 2). The FDA alleges that GSK used several tactics, such as printing and distributing literature which misrepresented a clinical trial showing the efficacy of the drug in patients under the age of 18, when the clinical trial did not, in fact, demonstrate efficacy (Office of Public Affairs, 2012, July 2). GSK also was believed by the U.S. Government to have promoted Wellbutrin, a drug approved for major depression disorder, for “weight loss, the treatment of sexual dysfunction, substance addictions, and Attention Deficit Hyperactivity Disorder, among other off-label uses” (Office of Public Affairs, 2012, July 2, 1). To promote these unapproved uses, GSK was believed to have sponsored many health care professional events, paid doctors to speak at events, and created advisory boards (Office of Public Affairs, 2012, July 2). In addition to these and other violations pertaining to Advair, Lamictal, and Zofran, GSK agreed to pay an unprecedented total \$3 billion (Office of Public Affairs, 2012, July 2). When speaking of these large figures, however, included in them is the amount paid in civil liabilities to government and state agencies for allegations related to the False Claims Act, because non-compliance is doubly costly in many instances.

Government Health Program Fraud

Of all the major non-compliance occurring in the industry, fraudulent practices involving U.S. government and state health care programs are considered some of the most costly forms of non-compliance for the U.S. government. Several different points of non-compliance 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. As was said previously, 83% of recent major investigations have resulted in civil fines and forfeitures for

violating the False Claims Act. It also should be noted that, as Figure 3 (Appendix) 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, November 16). This can involve Medicare, Medicaid, Tricare, and any other health program paid for by tax payer money (American Cancer Society, 2012).

The contention of the government is that without the non-compliance, whether that be off-label promotion or false safety data reporting, physicians would not write so many prescriptions for a particular medication, which would result in fewer insurance claims and less money being spent by the health programs. 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, November 9). 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). Each of the previous cases discussed had a civil component to it, included in the larger monetary figure. In the large Pfizer case in which they agreed to a \$2.3 billion settlement, \$1 billion of that settlement was a civil fine that was split between federal and state governments (Pelofsky & Pierson, 2009). With GlaxoSmithKline's unprecedented \$3 billion settlement, \$2 billion was agreed to in civil fines and forfeitures (Office of Public Affairs, 2012, July 2).

TOO BIG TO COMPLY

Size matters - more than half of all major settlements between 2006 and 2010 were recovered from four of the Top 10 revenue-generating companies of 2010 (Giniat, 2011). Table 4 (Appendix) shows the 10 largest government settlements in the history of the pharmaceutical industry. When calculated, these seven companies were ordered to pay more than \$12.6 billion. However, when revenue of these companies in 2010 alone amounted to \$235 billion they were only required to pay just over 5% of their revenues (Giniat, 2011). Defiance pays well, particularly since large firms can offload risk throughout the supply chain, particularly by using foreign contract research firms (Braithwaite, 2013; Gagnon, 2013).

While the supply chain is the accurate level of analysis, data is primarily gathered by organization. The Top 10 pharmaceutical companies in revenue received 15% of all letters issued during that period of time 2003-2012, with an average of nine letters issued per company (Cacciotti & Clinton, 2011; U.S. Food and Drug Administration, 2012, September 7). These Top 10 companies generated a combined revenue of \$352.6 billion in 2010 (Cacciotti & Clinton, 2011). The Top 11-50 companies were issued an additional 13% of letters, for a greatly reduced average of two letters per company. The combined revenue in 2010 of these 40 companies was estimated at \$241.1 billion (Cacciotti & Clinton, 2011). The outstanding 72% or about 450 of letters issued between 2003 and 2012 were spread out within the remaining thousands of pharmaceutical companies in the world. Figure 4 (Appendix) shows the slight correlation between the amount of revenue for each company and the number of letters received. Continuing to follow the research methodology, an analysis of CIAs showed that 35% of the Top 50 companies by revenue are currently under terms of a CIA (Office of Inspector General, 2012). Further, eight of the Top 10 pharmaceutical companies by revenue are currently working under a CIA (Office of Inspector General, 2012).

The relationship between non-compliance and revenue is much clearer concerning off-label advertising. The OPDP issued most of the FDA warning letters with over half of those letters going to the Top 50 revenue-generating pharma companies. Some 95% of letters issued to the Top 10 companies were given for marketing promotions (U.S. Food and Drug Administration, 2012, November 29). The relationship between letters and revenue is illustrated in Figure 5 (Appendix).

True, companies with more visibility, larger advertising budgets, and more marketing personnel may have an increased susceptibility to being targeted for promotional non-compliance. However, profit motive should not be overlooked. For example, Johnson & Johnson agreed to pay \$1 billion for off-label promotion practices for their popular drug Risperdal, representing just 4% of total worldwide revenue of the drug from 2003 to 2010 (Cronin Fisk, Feeley, & Voreacos, 2012, September 7). Table 5 (Appendix) shows just a few examples of the largest settlements in recent years versus the companies' total profits in the year of the settlement.

A detailed description of compliance as a profitable, legal strategy is outlined in Bird & Orozco (2014). These authors also define in detail the pros and cons of using the additional legal strategies of avoidance, prevention, value, and transformation. It appears that as the FDA moves more to incorporate a quality focus across its policies and regulations, it may be entering a turning point into greater emphasis on some of these other four strategies.

REGULATORY EVOLUTION

The FDA claims to have taken notice. HHS OIG Chief Counsel Lewis Morris explained to congress in 2011 that "Providers that engage in health care fraud may consider civil penalties and criminal fines a cost of doing business...It's not that drug makers don't know the risks; they've just decided that the rewards outweigh them" (McCarthy, 2012, 14). Consequently, the FDA is trying to promote compliance by creating new compliance programs and innovative enforcement actions to non-compliance, based on the eight propositions listed below.

Proposition 1: Rates of Non-Compliance Decrease as the Size of Fines and Penalties Increase.

Fines and penalties have increased to record levels. Table 5 (Appendix) compares companies' total profits to settlement values. While settlements did take a significant portion of these companies' profits, researchers have remained skeptical concerning their potential deterrent effect (Braithwaite, 2013; Light, Lexchin & Darrow, 2013; Mansfield, 2005).

Proposition 2: Rates of Non-Compliant Off-Label Promotion Decrease as the Size and Sophistication of FDA Scrutiny of Drug Marketing Increases.

The FDA has increasing scrutiny on the promotion and marketing of drug products to prevent scandals (Mintzes, et al., 2013) such as Depakote. Abbott maintained a dedicated sales force to market Depakote 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, May 7). Now, the FDA is expanding the scope of its investigations to include the Internet and marketing on social network sites and even electronic games wherein the hope is to attract

the attention of tech-savvy millennials who have grown up with apps and mobile technology (Zwick, 2012; Chaudhry, 2011; Weschler, 2012, March; Drell, 2014). Fines are also increasing, for example, of the \$1.5 billion that Abbott Labs paid for their off-label promotion of Depakote, \$800 million was paid to state and federal governments for unapproved uses of the medication for government health care recipients (Office of Public Affairs, 2012, May 7). Since these efforts demand resource allocation in a chronically underfunded agency (Light, et al., 2013), their current and future effectiveness is problematic.

Proposition 3: Rates of Non-Compliance Decrease as the Penalties for Drug Maker Executives Responsible for the Infraction(s) Increase.

New FDA regulations call for direct oversight by corporate executives, so they can be held accountable (Pickett, 2011). The Park Legal Doctrine holds corporate executives liable for FDA violations (Weschler, 2012, February) and the Herger-Stark Proposal “would allow HHS to ban executives from working with Medicare and Medicaid if they are convicted, regardless of where they currently work a death knell for anyone in the health industry” (McCarthy, 2012, 14; Zwick, 2012). For example the CEO of KV Pharmaceuticals, Marc Hermelin, agreed to pay \$1.9 million in fines and forfeitures and spend one month in jail and was banned from future participation in Medicare and Medicaid programs after it was discovered that, under his direction, KV had manufactured and shipped inaccurately dosed and sized tablets. (U.S. Attorney Eastern District of Missouri, 2011) The deterrent effect of such provisions will depend on the penalties matching or exceeding the compensation such executives received for these infractions (golden parachutes, bonuses, stock options, etc.) (Light, et al., 2013).

Proposition 4: Rates of Non-Compliance Decrease as the Potential Loss of Market Access Increases.

HHS OIG Corporate Integrity Agreements (CIAs) are beginning to have 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, 14). This threat is viable, so long as it is occasionally used, and does not remain a paper tiger.

Rates of regulatory compliance also tend to increase when they are linked to rates of customer satisfaction and loyalty. One’s consumers need to be satisfied or else they will leave and go elsewhere, and market share and access consequently will be lost. “The patient - rather than the bottom line - must be in the minds and goals of management at all times in order for a sense of ownership and responsibility to trickle down” (Drakulich, 2011, 14). Thus, action will be increased when regulatory complaints align with common consumer complaints including (Asotra, Cossin, & Yacobi, 2012, 112):

- There are difficulties in dispensing due to abnormal flow of a semi-solid product from a tube or visual changes in appearance, such as separation or discoloration.
- The tablets are chipped, discolored, or pigmented and may show capping or other visual defects.

- Hard-gel capsules may clump together and the pharmacist or consumer is unable to separate without compromising the individual capsule integrity.
- A nasal spray product when dispensed does not flow as a uniform spray.
- There are particulates or precipitation in injectables or solutions.

Proposition 5: Rates of Non-Compliance Decrease as the Frequency of Enforcement Actions such as Inspections Increase.

Currently, this involves doubling the frequency of drug company inspections with better trained FDA examiners. Particular attention will focus on the quality of the supply chain. Approximately, 30 percent of drug maker inspections now are taking place outside of the United States (Zwick, 2012). Given the chronic underfunding of the FDA, critics applaud the goal, but challenge whether it can be realistically implemented (Braithwaite, 2013; Furberg, Levin, Gross, Shapiro, & Strom, 2006).

Proposition 6: Rates of Non-Compliance of Foreign Drug Makers Decrease as the Frequency of Enforcement Actions such as Inspections Increase, Either by the FDA or Foreign Partners.

The FDA is pursuing international collaboration, such as the FDA and EMA (European Medicines Agency) announcement of a new GMP (Good Manufacturing Practices) inspection initiative that calls for “sharing information on drug-manufacturing inspections in their respective regions” (Wechsler, 2012, 1; Schnoll, 2014). Further the PIC/S, or Pharmaceutical Inspection Cooperation Scheme, a collaborative effort by over 40 nations (soon to include India and China), is being developed to “facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of GMP inspectors” (PIC/S, 2012, 1; Wechsler, 2012). It is too soon to evaluate their performance.

Proposition 7: Rates of Non-Compliance Decrease as the Clarity of FDA Standards Increase.

The FDA has initiated programs to increase efficiency, such as international collaborative programs by the FDA and EMA “to streamline the review of manufacturing data in drug applications” (Wechsler, 2012, 11). Domestically, the Generic Drug User Fee Amendment (GDUFA) is “designed to speed access to safe and effective generic drugs to the public and reduce costs to industry,” although the cost savings have proven problematic (Food & Drug Administration, 2012, 1; Wechsler, 2012). It is too soon to evaluate their performance.

Proposition 8: Rates of Non-Compliance Decrease as the Authority of Dedicated Compliance Departments Increase.

The FDA has encouraged the increasing authority of compliance personnel, such as having compliance officers report directly to the CEO in their company. Organizations large and small have seen an increased need to show regulatory agencies that they understand the importance of having a strong and visible compliance department (Biskup, 2012). The need for

a strong compliance department is indiscriminate to the size of the company, as all corporations in this industry are subject to audits and inspections (Zwick, 2012). Given that compliance departments are developed by senior managers, their effectiveness reflects the attitudes of their superiors concerning compliance.

Codes of ethics also can be used to support the compliance personnel and officers, the compliance department, and senior management (Anghel-Illcu, 2014, 111):

“Codes of ethics encompass companies’ vision on business conduct and ethics in relation with its stakeholders. Presenting a code of ethics is rather a voluntary process, therefore a large amount of heterogeneity is found among such codes. A general model of code of ethics...is focused on specific categories of stakeholders: capital owners (shareholders and investors), management, employees, customers, suppliers, subcontractors, governments, communities, and the environment.”

Hence, pharmaceutical companies need to focus on effective and efficient relationship with and results for each of these stakeholders.

IMPLICATIONS

Many analysts allege that the measures described above are too little, too late. Regulators cannot match the motivation and ability of their corporate counterparts to effectively deter non-compliance. At this point, criticisms focus on three areas - conflicts of interest, inadequate enforcement, and inadequate deterrence. How these issues will be managed and resolved remains a subject of considerable debate.

Conflicts of Interest

Now that the FDA has become dependent on industry safety studies and corporate user fees, critics allege the agency is in the process of being “captured” by Big Pharma. A revolving door of regulators becoming lobbyists with lucrative contracts has secured favorable treatment - meeting the needs of the drug companies seems to command higher priority than maximizing public health and safety (Brezis & Wiist, 2011; Furberg, et al., 2006; Light, et al., 2013; Mansfield, 2005). However the cost of independent clinical trials is prohibitive, and securing independent FDA leadership would require unlikely Congressional legislation.

Major pharmaceutical companies dispute these claims, noting that in the absence of clear, consistent, and effective regulations, it is their stakeholder obligation to shape this chaos into regulation which can be implemented effectively and efficiently (Huberman Arnold, Arnold, & Arnold, 2010, 1):

“When economic conditions are negative, organizations look to legislation, regulations, and codes, to reform their culture, and manage the risks of organizational failure. Both the compliance strategy, demanding obedience to laws, regulations and codes, and the integrity or values strategy, focusing on ethics training, education, tone at the top, and the hiring of employees with integrity and values, are the mainstay of recent legislation and regulations in North America and the European Union. We criticize the reliance on legislation, regulations and codes, the focus of a compliance solution which we find inadequate, ineffective, and unenforceable. We suggest reliance on a front-end, proactive and preventive program of best, pre-cautionary practices, will better meet the challenge, in prosperity or poverty, of setting corporate culture on the right track.”

Inadequate Enforcement

The current FDA systems and structures have chronic problems. The agency is perpetually under-funded, making the burden of under-funded legislative mandates impossible to fulfill. Further, 28 percent of FDA resources are eligible to retire by fiscal 2015 (Partnership for Public Service, 2012). If cuts or funding plateaus occur now or in 2015, then the following are likely to occur:

- Food will be less safe and consumers put at risk.
- Drug and device reviews will be slower, conflicting with promises made to consumers and companies.
- Problems with imports and globalization will become more numerous.
- Critical efforts to modernize the agency and improve its innovation will stall. (Dorman, 2013)

Additionally, what staff are available often lack in training and expertise to perform effectively, particularly given the time constraints (Furberg, et al., 2006). This means that adequate oversight of drug trial designs, reporting of adverse events, and post-marketing surveillance systems all become problematic. Also, the cost of full public funding for all FDA activities and the creation of a National Drug Safety Board is enormous.

However, it is interesting to note that more recent operational changes and a paradigm shift at the U.S. Food and Drug Administration are occurring and are scheduled to occur into the future to supposedly provide more effective deterrence and guidance. If funded, the operational changes are scheduled to be laid out in a five-year Pharmaceuticals Action Plan that will be developed in 2015 by ORA (Office of Regulatory Affairs), CDER, and the Centre for Veterinary Medicine (CVM) (Weschler, 2014, 20-21):

“[To improve] alignment between FDA and European inspection field forces...a new Programme Alignment Group (PAG) plans to integrate more closely centre and field oversight functions through ‘commodity-based and vertically-integrated regulatory programmes.’ At the same time, the Centre for Drug Evaluation and Research (CDER)...is establishing a new ‘super’ Office of Pharmaceutical Quality (OPQ) [for a]...‘one voice for quality’ approach that coordinates review, inspection, and research activities related to drug quality...[It emphasizes] the importance of moving from a ‘rule-based’ to a ‘risk-based’ approach based on common understanding of what constitutes real risk in pharmaceutical products. Field inspections will shift from ‘writing traffic tickets’ to full product assessment - not just negative observations but what the manufacturer is doing well. This intelligence will support a ‘pharmaceutical platform’ with a complete inventory of regulated facilities around the world (e.g., location, ownership, products, surveillance information).” (Zonnenberg, 2014, 42):

Inadequate Deterrence

There is critical consensus that penalties matter most only when the fines involved match or exceed the profits gained from the infraction. To the extent that the FDA becomes a paper tiger, deterrence will be minimized (Brezis & Wiist, 2011; Furberg, et al., 2006). For example, manufacturers do not fulfill the majority of their post-marketing safety study commitments, but the FDA lacks the authority to pursue and punish the offenders (Light, et al., 2013; Mansfield,

2005).

The Vioxx case epitomizes the problems faced by drug enforcers, being one of the only cases in which there was proof that employees at a company knowingly defied regulations and guidelines. Results from a contracted study that suggested the need for an outcomes trial were ignored, with one Merck scientist stating “a trial with that design would kill the drug” (Nesi, 2010, 111). The New England Journal of Medicine discovered discrepancies in both major trials for Vioxx, including the deletion of “3 heart attacks in the Vioxx group, greatly improving the outcome” (Nesi, 2010, 128-129). And it was later proven that one of the most influential studies that was passed off as double-blinded, the VIGOR study, was in reality completely unblinded, with one of Merck’s statisticians, Dr. Deborah Shapiro, knowing exactly which patient was on which medication, and analyzing the data accordingly (Nesi, 2010).

While Vioxx made money in the short-term, the long-term picture challenges the financial benefits of non-compliance. Merck & Co. paid over \$4.8 billion for the product liability litigation and over \$7.7 billion on settlements and legal costs (Randall & Voreacos, 2010), compared to an estimated \$11 billion in sales (FiercePharma, 2012). This comparison does not include damage to reputation and the effects of the negative publicity on stock prices. In this instance, it is hard to believe that Merck & Co. came out ahead due to so many secondary factors effecting the situation.

Consequently, it takes a “perfect storm” to disrupt the business case for non-compliance:

- The non-compliance must be reported and publicized instead of repressed or white-washed.
- The defiance must be serious enough to provoke a significant response from the FDA, despite the impact of under-funding on enforcement.
- The negative side effects have to be serious enough to generate a great deal of litigation.
- The long-term, as well as short-term financial impacts must be significant enough to factor into strategic and senior management compensation decision-making.
- Above all, the total bill from negative primary and secondary repercussions must erase profit.

Problems of this magnitude are relatively rare, and enforcement is decreasing. Figure 6 notes the enforcement trends in OPDP, which issues more warning letters than any other drug related department.

CONCLUSIONS AND FUTURE OUTLOOK

As the strategies of pharmaceutical companies evolve, Crommelin, Stolk, Besancon, Shah, Midha, & Leufkens (2010) suggest four possible trajectories looking towards 2020:

1. Filling the pipeline - Pharmaceutical companies remain dominant in innovation, with SMEs (Small and Medium-Sized Enterprises) as suppliers of early-stage developments, and governments are partners through PPPs (Public-Private Partnerships). Regulation is strongly driven for harmonization, with regulators faced with high-tech and complex technologies.
2. Fusion - Traditional pharmaceutical companies decline as the life sciences become more focused on devices and lifestyle technologies. New types of businesses emerge at interfaces, while there are major challenges for regulators to globally integrate

- regulations on various combinations of technologies. This leads to a strong drive for harmonization.
3. Pharmaceutical expenditure constraints - There is strong pressure to contain drug prices in major markets, with companies focusing on niche markets in which added value can be shown more easily. There is little global harmonization and payers focus on cost reduction. Mechanisms are tested for 'gradual' market authorization for new drugs.
 4. Decline of the titans - A large part of drug development takes place in publicly funded institutes, in parallel with SMEs. Pharmaceutical companies exist for confirmatory trials, production, and regulatory approval. Regulators are crucial administrators as society has become strongly risk averse. There is a limited drive for global harmonization.

The strategic viability of compliance versus defiance rests with growth patterns in organizational size. The larger the firm, the greater the tendencies towards regulatory defiance. SMEs usually provide specialty pharmaceuticals, with a market value of \$21 billion in 2009. There are more than 80 companies actively participating in this specialty market, with more than 550 specialty pharmaceutical products marketed in the US. These companies typically have small to medium-sized sales forces that promote products with annual sales of less than \$200 million. Small to medium-sized specialty companies tend to in-license late-stage or under-promoted products in therapeutic categories ripe with an opportunity for revenue growth. Overall, in 2009, the top-selling specialty pharmaceutical products were products for pain, sleep disorders, opioid dependence, and ADHD. So, essentially, many small to medium-size companies are in niche markets in order to survive against the big pharmaceutical companies. (Research and Markets, 2011) If larger firms invade niche markets, strategic defiance may become a strategy of choice, and compliant SMEs will face escalating disincentives and problematic sustainability. Major demotivators focus on economies of scale, particularly in advertising:

- Increasing costs of direct-to-consumer advertising (DTCA) which larger companies can absorb (and any consequential fines or costs) much more easily than the smaller or medium-sized companies. Consequently, advertising in 2008 was at 4.2 billion dollars, down from 5 billion dollars the year before (Macias et. al., 2010; Goldberg, 2013).
- Increasing costs of physician uptake advertising, involve high levels of marketing exposure through broadcast, network media, advertisement language, and advertisement duration, as well as opportunities for intense communication with colleagues (Al-Dmour, Al-Zu'bi, & Fahmawi, 2013; Lublóy, 2014). In 2012, drug promotions to physicians totaled \$24 billion (Cegedim Company, 2013; Reisin-Miller & Rockwell, 2013). (The Pew Charitable Trusts, 2013)

When viability is threatened, compliant SMEs may be forced to conform to norms of non-compliant large firms they are forced to deal with. Strategic alliances with large firms can be vital to the survival and growth of small firms, while offering legitimacy, reputation, and complementary resources. Or the large company may tend to outlearn or exploit the small firms and take away a bigger proportion of the value created in the alliance. "In general small firms can derive greater benefits from exploitation alliances than from exploration alliances with large firms. However, if small firms manage their alliances with large firms via proper alliance governance, they will enhance their value from exploration alliances with large firms" (Yang,

Zheng, & Zhao, 2014, 146). Exploration alliances often provide the small firm with new opportunities, new competencies, and better adaptation to the environment. Exploitation alliances tend to leverage a small firm's existing capabilities and combine competencies across organizational boundaries. (Yang, Zheng, & Zhao, 2014). If these trends continue, consolidation may dramatically reduce the presence of SMEs:

“The past decade has witnessed significant consolidation within the pharmaceutical industry - most recent megadeals include Pfizer's acquisition of Wyeth, and Merck's merger with Schering-Plough. The recent cash shortage at young bio-pharmaceutical firms presents investment opportunity for cash-rich big pharmaceutical firms to replenish their drug development pipeline at bargain prices.” (Zhang, 2012, 200)

With the winnowing of SMEs and the weakening of FDA enforcement, strategic defiance is not only common, but is supported by the chronic and deliberate underfunding of the FDA. The question arises if indeed the FDA has adopted a strategy of crisis prevention and management versus the broader mission of general public health and safety. Consider this composite crisis management model: pre-crisis problem incubation, prevention, and preparation; crisis damage control and blame; post-crisis damage assessment, stabilization, problem resolution, system adjustment, and marketing (Fragouli, Ioannidis & Adiave, 2013; Jordan-Meier, 2011; Mitroff, & Pearson, 1993; Penrose, 2000; Rike, 2003). Increasingly, pre-crisis efforts seem token and the emphasis is on post-crisis activities to reassure the public by making an example of a truly egregious wrongdoer. Further research on these issues is important unless society is willing to institutionalize strategic defiance as a common strategy for large drug companies in an increasingly self-policing pharmaceutical industry.

Pharmaceutical companies insist that such decisions be placed in context. The aging of the population, high prevalence of chronic and new diseases, new discoveries and (bio)technologies, healthcare reform, and increased need for evidence-based practice are all factors of high impact and change to the pharmaceutical industry (Masri, Ramirez, Popescu, & Reggie, 2012). They also are quite expensive, forcing uncomfortable tradeoffs between quality and affordable care. While the major stakeholders involved insist on high quality, they also insist these goals be pursued in the context of a cost-benefit analysis. Strategic non-compliance of unreasonable regulations allows for pragmatic compromises between these conflicting goals. Given that a strong pharmaceutical industry is very important to the quality of life and happiness of everyone, this balancing act between optimal and satisfactory goals remains a tension to manage, and periodically re-examine, rather than resolve.

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APPENDIX: TABLES AND FIGURES**Table 1****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 non-compliance observed
U.S. Department of Justice (U.S. DOJ)	Criminal and Civil Litigation and Settlements	Quantifies non-compliance by monetary value	Does not always reflect non-compliance 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 non-compliance	Not typically issued to smaller companies or outside of litigation/settlements

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	ODLDC	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)

Table 3
cGMP Violations in 2009

Date	Company	Action	Problems	Penalties
April 2009	Advent Pharmaceuticals	Consent Decree, permanent injunction	GMPs, selling unapproved drugs	Up to \$1 million per year for 6 years
April 2009	Shanghai No. 1 Biochem and Pharma	Warning Letter	GMP, documentation	
April 2009	Qingdao Jiulong Biopharma Co.	Warning Letter	GMP, failure to investigate contaminated heparin	
April 2009	Cipta	483	GMP	30 days to rectify
March 2009	KV Pharmaceuticals	Consent Decree	GMP, selling unapproved drugs	Up to \$5 million per year per violation for 6 years
March 2009	Xanodyne, Roxane Labs, BI-Roxane, Cody Labs, LehighValley, Mallinckrodt, Glenmark, Lannett, Physicians Total Care	Warning Letter	Selling unapproved new drug	
Feb. 2009	Genzyme	Warning Letter	GMP, aseptic manufacturing, training, IT	
Feb. 2009	Taro Pharmaceuticals Prime Labs	Warning Letter	GMP	

Table created from data published by Agnes Shanley (Shanley, 2009).

Table 4
Largest Government Settlements

Company	2010 Revenue (in billions)	Settlement Value	Violation	Date
Merck	\$39.80	\$4.8 billion	Drug Safety	July 28, 2010
Pfizer	\$58.50	\$2.3 billion	Off-Label Promotion	September 2, 2009
Eli Lilly	\$21.10	\$1.4 billion	Drug Safety	January 14, 2009
GlaxoSmithKline	\$36.20	\$1 billion	Drug Safety	December 14, 2009
GlaxoSmithKline	\$36.20	\$750 million	Adulterated drugs	October 26, 2010
Allergan	\$4.00	\$600 million	Off-Label Promotion	September 2, 2010
AstraZeneca	\$33.30	\$520 million	Off-Label Promotion	April 27, 2010
GlaxoSmithKline	\$36.20	\$460 million	Drug Safety	July 14, 2010
Novartis	\$42.00	\$422.5 million	Off-Label Promotion	September 30, 2010
GlaxoSmithKline	\$36.20	\$400 million	Off-Label Promotion	January 30, 2009

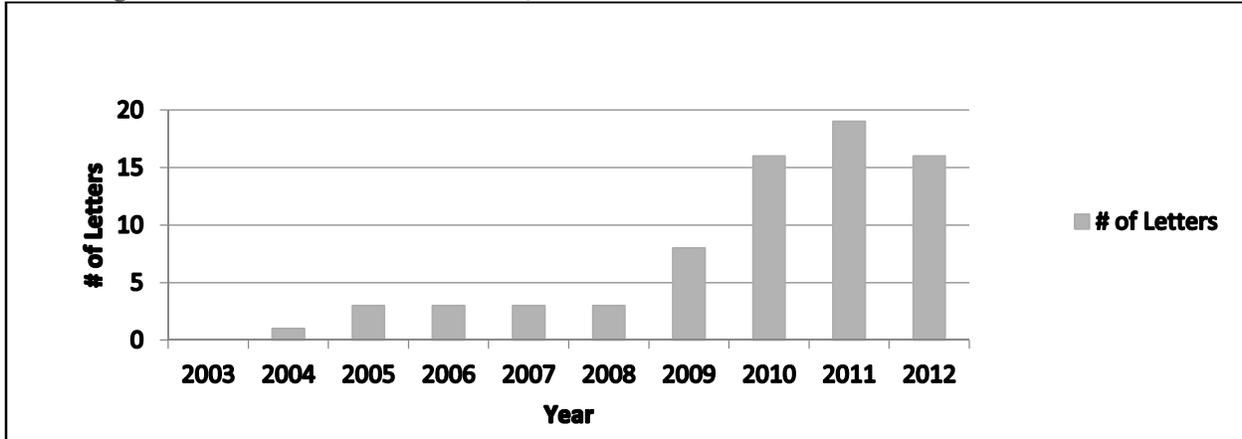
Table created by Ed Giniat (Giniat, 2011).

Table 5
Major Settlement Values vs. Total Profits

Company	Settlement Value	Total Profits	Settle Value as Percentage of Profits
Merck & Co.	\$4.8 billion	\$8.1 billion (2007)	59%
GlaxoSmithKline PLC	\$3 billion	\$8.2 billion (2011)	37%
Pfizer, Inc.	\$2.3 billion	\$11.4 billion (2008)	20%
Eli Lilly & Co.	\$1.4 billion	\$3.4 billion (2008)	41%

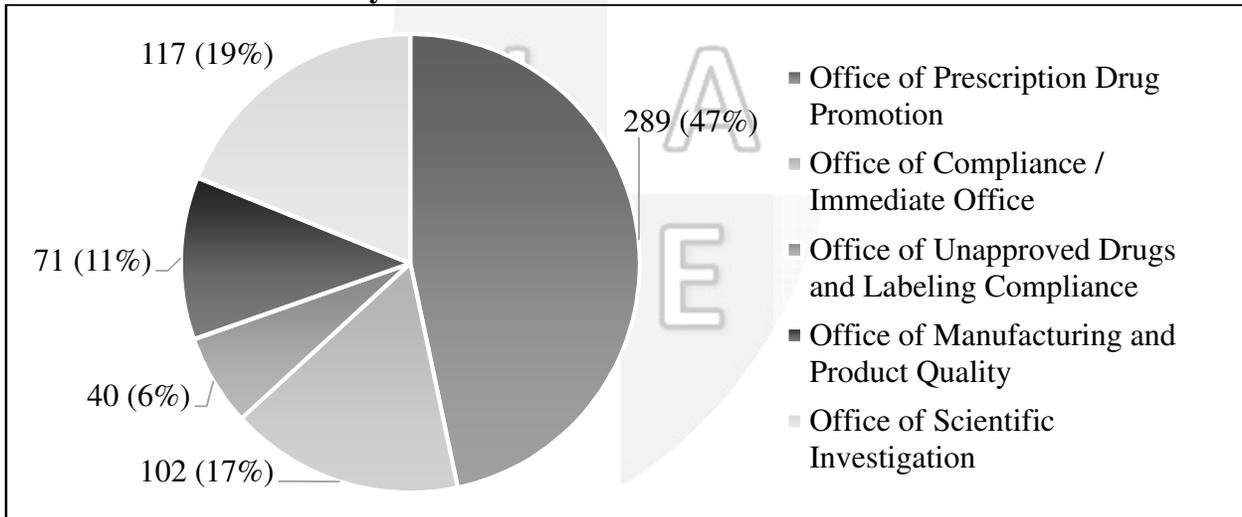
Original table created with information gathered from the following sources: (Eli Lilly & Co., 2012; Giniat, 2011; GlaxoSmithKline PLC, 2012; Merck & Co., Inc., 2012; Pelofsky & Pierson, 2009; & Pfizer, Inc., 2012.

Figure 1
Warning/Untitled Letters from OMPQ



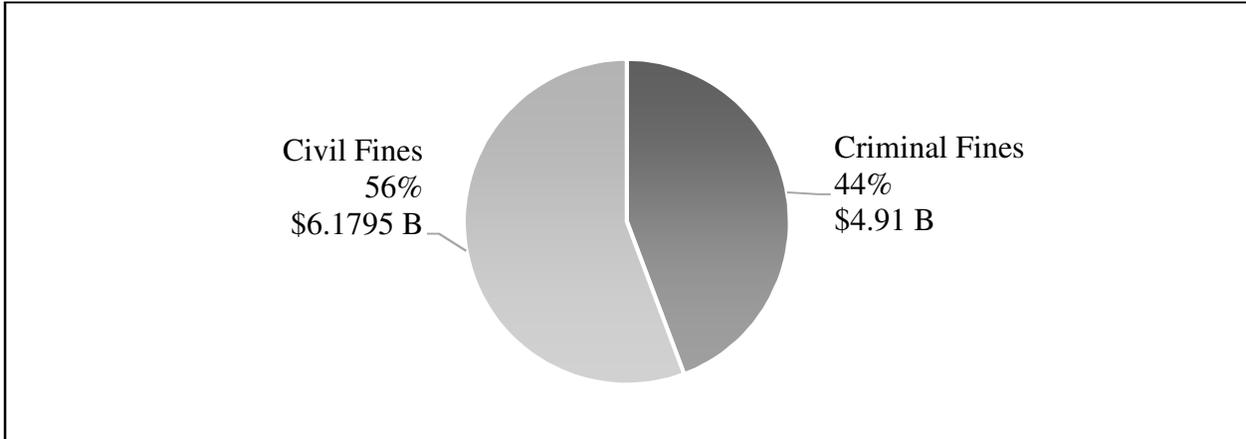
Original figure made from data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012).

Figure 2
2003-2012 Letters Issued by Office



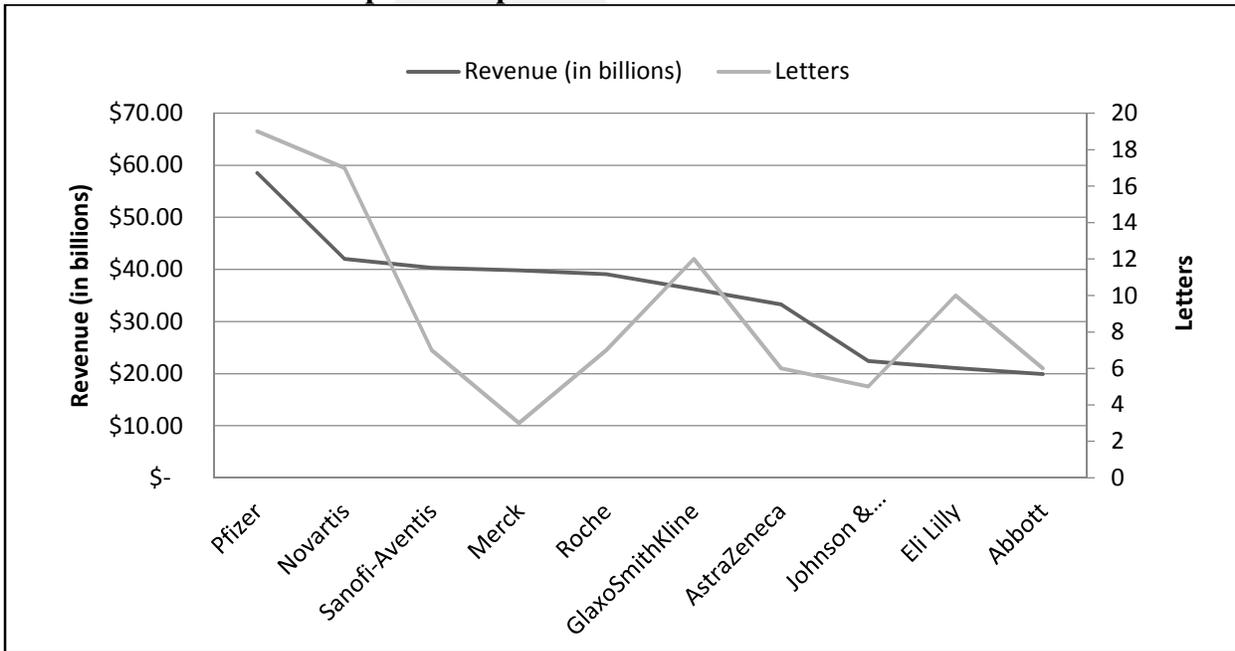
Original figure created with data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012).

Figure 3
Criminal vs. Civil Fines 2009-2012



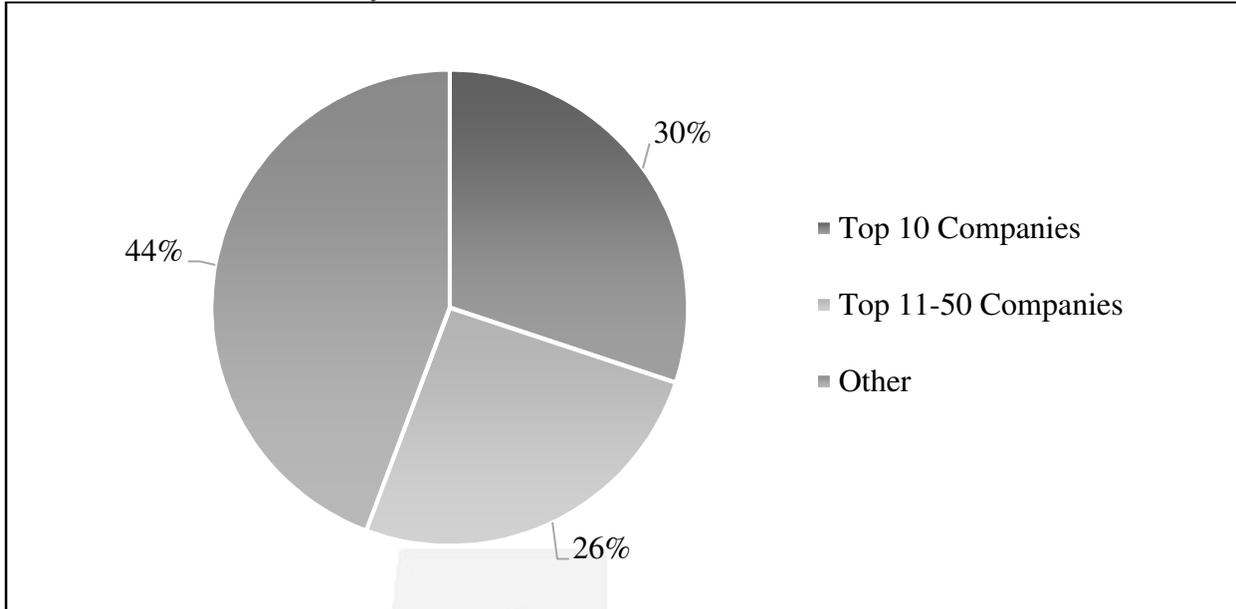
Original figure created with data compiled from U.S. FDA website (U.S. Food and Drug Administration, 2012).

Figure 4
Revenue vs. Letters for Top 10 Companies



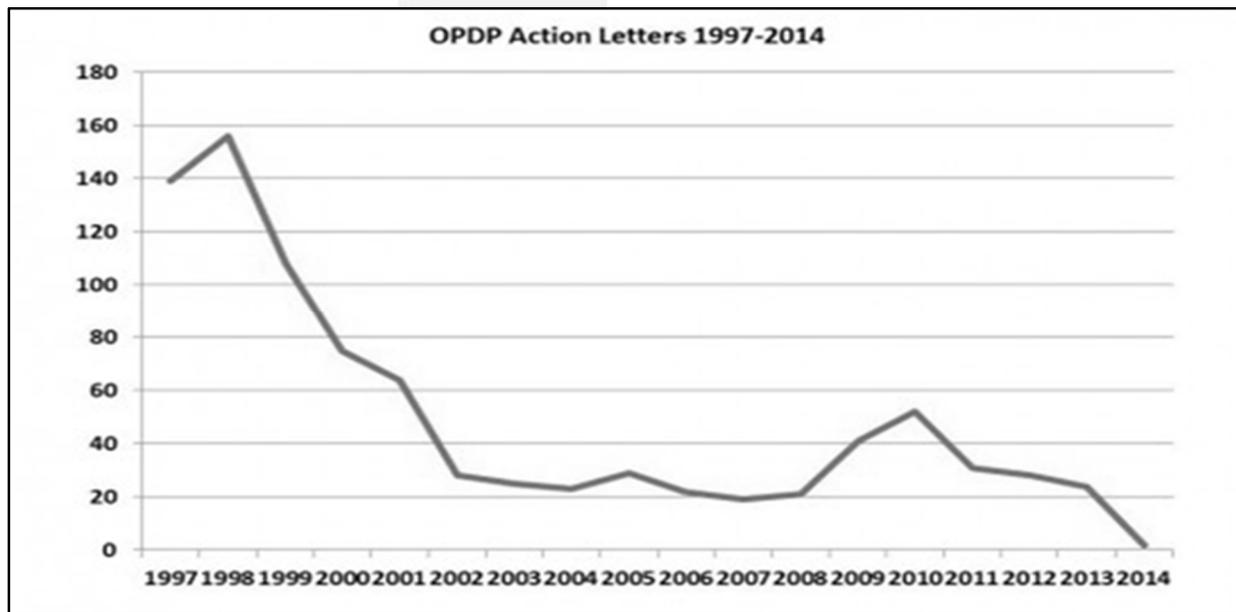
Adapted from <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm>.

Figure 5
2003-2012 Letters Issued by OPDP



Adapted from <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm>.

Figure 6
OPDP Action Letters 1997-2014



Adapted from U.S. Food and Drug Administration (2014, October 10). OPDP regulatory information. *U.S. Food and Drug Administration*. Retrieved from <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm>.