Monetary Incentives for Producing Counterfeit, Adulterated, and Misbranded Medicine: Case Studies and Examples

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ABSTRACT

Background: Pharmaceutical fraud can be very profitable. Those working in pharmaceuticals are in a tempting position as the nature of the product and supply is complex, making detection of fraud difficult and expensive. However, a reliable pharmaceutical supply can often be a life-or-death situation for patients. Thus, when detection of fraud occurs, a Regulator's Dilemma often emerges (recall a drug for which a supplier is the sole source, or allow a substandard product to be sold)—generally resulting in pharmaceutical companies receiving minimal penalties even for the worst acts. Despite pharmaceutical companies' unique leverage over regulators and profitability, studies are rare in the scientific literature regarding pharmaceutical fraud.

Purpose: The primary aim of this article is to increase awareness of the various types of pharmaceutical frauds. In addition, the secondary objective is to provide insight into the influence economics possesses in motivating pharmaceutical fraud.

Method: Case studies and examples of pharmaceutical fraud are described. Reviewed case studies include purchasing and distribution of products from unlicensed sellers, unlawful promotion of Paxil, Wellbutrin, and Avandia, and concealing bladder cancer risk associated with pioglitazone. Economic information is gathered through mining the US Department of Labor Statistics, Govinfo, US Securities and Exchange Commission, companies annual reports, and US Department of Justice databases. Economic screenshots are used to summarize the frauds surrounding economics both within and external to the companies.

Results: Purchasing and distribution of products from unlicensed sellers occurred between December 2006 to August 2009 and took place solely in the US. Economic snapshots of this time show that the US was in an economic recession. During this time raw material costs were high and the pharmaceutical industry was experiencing major lay-offs. The scheme resulted in the company grossing over $50 million-dollar in added proceeds.

The unlawful promotion of Paxil, Wellbutrin, Avandia, Avair and others occurred between 1998 to 2010 on a global scale. The economic snapshot of this time shows the company faced patent expiration of several highly profitable patents during this period, starting in 1997 with Zantac's expiry and then with the loss of Augmentin in 2002, several years before its patent expiration of 2018. Avandia lost market exclusivity in 2008 and Advair lost market exclusivity in 2010. The company also faced several regulatory challenges. In addition, more than one economic recession occurred during this time including the Asian and US markets. Finally, the concealment of cancer risks with pioglitazone occurred from the approval of the drug in 1999 to the settlement in 2015. Between 1995-1999 the company was growing and had launched several worldwide ventures. In addition to expanding, the company faced regulatory black-box challenges as well as encountering recessions in the US.

Conclusions: History suggests that monetary incentives are motivators in unethical behavior and fraud cases. Economic recessions, patent expirations, and company expansion are among the most consistent economic pressures surrounding the cases studied, suggesting these variables may be predictors of potential drug quality issues.

Keywords: *fraud incentive, pharmaceutical fraud, economics of fraud, deception, concealment*

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1 INTRODUCTION

In 1996, Ritonavir was approved to market as a protease inhibitor ("Ritonavir, Abbott protease inhibitor, approved.," 1996). By 1998 Abbott Laboratories was facing a potential financial crisis as a less soluble polymorph (Form II) of Ritonavir was discovered (Bauer et al., 2001) forming during the manufacturing process of Ritonavir. The detection of Form II resulted in a temporary halt in Ritonavir sales. In addition to the loss in sales and "ticking clock on" patent life, Abbott Laboratories also faced additional development costs (Aldridge, 2007; Bauer et al., 2001). Abbott Laboratories scientists ultimately found methods to avoid the polymorph formation, and Ritonavir was returned to market. Nevertheless, Abbott faced a significant financial burden due to this unexpected event.

Ritonavir's unforeseen polymorphic change is an example of the complexities and risk involved in pharmaceutical development. Analytical techniques such as Raman spectrometry, solid-state nuclear magnetic resonance, and x-ray diffraction are used to identify polymorphs before a drug is approved (Bauer et al., 2001). In addition, computational modeling is achieving some success in predicting polymorphs early in the development process (Piaggi and Parrinello, 2018). However, these techniques can only be helpful if the parties involved are honest. This seems to be the case with Abbott Laboratories' and Ritonavir. Unfortunately, companies (humans) are not always honest in stressful scenarios. Honesty is potentially expensive in terms of time and money, possibly incentivizing humans to decide on a dishonest, unethical, or fraudulent path.

When companies face difficult choices, the humans leading those companies must decide to act ethically or unethically. When a dishonest path is chosen, fraud is the result. Fraud can be described as an intentionally deceitful action intended to provide dishonest gain (Chen and James, 2021). Criminology tells us that in order to effectively detect fraud, pursuers must know why it's committed (Kassem and Higson, 2012). The Fraud Triangle Theory of criminologist Donald R. Cressey shines a light on this topic. Cressey theorized that for fraud to occur, three elements must be present: incentive, opportunity and rationalization (Cressey, 1973). Examining the pharmaceutical industry through the fraud triangle, we see an ideal environment for fraud emerge.

Incentive: The pharmaceutical industry's 2006 global sales totaled approximately $634 billion. This value is almost double the 2001 global sales of $387 billion (OECD, 2008). In 2010, counterfeit drugs (defined below) were worth an estimated $75 billion. Moreover, the profit margins for counterfeits are reported higher than illicit drug trafficking (Chambliss et al., 2012). For example, counterfeit sildenafil (Viagra) is estimated to be nearly ten times more profitable than street heroin (Everts, 2010), and nearly 2000 times more profitable than selling cocaine (Bingham, 2009). Providing plenty of monetary incentives for criminals. Indeed, actual criminals bypassing regulation and supply expenses, may gain 3000% increased profit margins than those who don't (Blackstone et al., 2014).

Opportunity: The globalization of the pharmaceutical industry has added complexity to the pharmaceutical development process and supply-chain (Luis Valverde, 2016). Further, the nature of the products is complex. Often requiring specialized equipment to detect contaminants (Campbell and Lodder, 2021). Collectively the complexity from the products and supply-chain makes detecting counterfeit, adulterated, and misbranded medicine (CAMM) difficult. Hence, providing a low-risk, high-opportunity environment for fraud.

Rationalization: Pharmaceuticals are sensitive in nature, which means life or death for many patients. This sensitivity may provide bad actors with the feeling they are doing good by providing vital products. Even if a few corners are cut, the important thing is the customer gets their drugs, right? Further, a unique relationship with regulators exists. Possibly allowing bad actors to rationalize avoiding penalties for their actions. For example, imagine a company producing an angiotensin II receptor blocker such as Valsartan is cited for policy incompliance. Regulators are then trapped in a regulator's dilemma. Shut the facility down until the violation is corrected. Therefore, risking a drug shortage in which thousands of patients could suffer (Jackevicius et al., 2020). Or allow the facility to continue producing the product with an agreement that the facility will fix the problem moving forward. With the latter option the most typical choice, the regulators are left having to rely on good faith alone. Allowing room for bad actors to easily rationalize penalty avoidance even if detection were to occur. Of course, this example is simplified. Indeed, regulator's dilemmas can be highly complex (Schilsky, 2018). Yet, the point remains. Pharmaceutical suppliers have a unique advantage over regulators. Hence, the sensitive nature of pharmaceuticals provides an environment for fraudsters to rationalize their bad actions.

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Satisfying each element of the fraud triangle the pharmaceutical industry provides an ideal environment for fraud to manifest. Pharmaceutical fraud is overarching and often refers to several unethical or dishonest acts. Indeed, it is not easy to define and has yet to find a universal definition. Health drug frauds, which are drug products that claim to treat disease or improve health with unproven effectiveness (FDA, 2016). And current good manufacturing practice (cGMP) incompliance in which pharmaceutical manufacturers knowingly (or unknowingly-this aspect being somewhat irrelevant as it is their legal responsibility to know) distribute low-quality products or fail to take the actions required to ensure quality (Rovira and Espín, 2009) are but two examples of what may be termed pharmaceutical fraud. To further complicate the ambiguous terminology, pharmaceutical counterfeiting, a common pharmaceutical crime, has found several definitions. For example, the world health organization (WHO) defined counterfeit medication as "one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and, counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."(WHO, 1999).While the FDA has simply referred to counterfeit drugs as "fake medicine" that may be harmful to one's health (FDA, 2011a). Further, WHO's attempts to update their definition have provided more confusion. Leading authors to often revert to the 1999 definition (Acri, 2018; Deisingh, 2005). Keen readers may have already noticed the overlaps in the WHO's 1999 definition of pharmaceutical counterfeits and the FDA's 2016 definition of health drug frauds. Nevertheless, for the purposes of this article, pharmaceutical fraud will be loosely defined as any intentionally deceitful action intended to provide dishonest gain through or related to pharmaceuticals and will be used to describe the actions which result in CAMMs. And unfortunately, CAMMs are a growing problem.

Pharmaceutical fraud is a growing issue. Indeed, WHO estimates that nearly 10% of the global pharmaceutical trade is counterfeit (Williams and McKnight, 2014). Further, counterfeits are no longer just an issue in developing regions of the world but a global concern (Wertheimer et al., 2003). In 2012, it was estimated that approximately 1% of drugs in the US were counterfeit, with an expected increase to occur annually (Chambliss et al., 2012). Though 1% seems negligible, Chambliss points out that if a pharmacy distributes 200 prescriptions a day. Two may be counterfeit (Chambliss et al., 2012). Recently, Valisure located in Connecticut reported that nearly 10% of the drugs tested have been counterfeit, adulterated, or misbranded (Valisure, 2021). Meaning out of 200 prescriptions 20 may be substandard. In other regions of the world, counterfeit drugs can make up to nearly 50% of the region's supply (Wertheimer et al., 2003; Williams and McKnight, 2014). In 2011, 64% of anti-malaria drugs in Nigeria were counterfeit (Blackstone et al., 2014). A quality assessment study of 7 cardiovascular drugs in 10 sub-Saharan countries found that of 1530 drugs tested, 249 were of poor quality. With amlodipine having the highest prevalence with, 87 of 305 samples deemed substandard. The study concluded that nearly 1 in 6 samples were counterfeit (Antignac et al., 2017). Truly pharmaceutical frauds are not a victimless crime. Indeed, reputable companies, partners, and patients are victimized.

CAMMs are particularly damaging to the reputable company. Indeed, piracy and counterfeits cost US companies nearly $200 billion annually and cost 750,000 jobs (Blackstone et al., 2014). Damages such as these have motivated companies to join the fight against counterfeits. For example, Pfizer’s partnership with law enforcement has prevented approximately 226 million counterfeits from reaching markets since 2004 (Pfizer, 2020). Additionally, Medsaf, a vitamin turn medicine manufacturer, has partnered with over 500 pharmacies and 100 hospitals to provide genuine medication to regions across Nigeria (Adeshokan, 2018). Though a great start, even one CAMM can be disastrous.

Pharmaceutical frauds can have catastrophic consequences for patients. In 2008, heparin batches possessing cheap contaminates in replacement of the API reached consumers. This resulted in a national recall but came too late for an estimated 83 patients who lost their lives (Blackstone et al., 2014). Similarly, 120 hospital patients in Pakistan lost their lives to contaminated Isotab. The isotab was reportedly contaminated with anti-malarial pyrimethamine causing rapid white blood cell depletion in its victims (Arie, 2012). Reports claim that CAMM kill nearly 100,000 annually in sub-Saharan regions alone (Adeshokan, 2018). A number that continues to rise (Atabong, 2021). Globally more than 500 children have died due to cough syrup contaminated with ethylene glycol (Liang, 2006). Nearly 155,000 children die annually due to poor-quality anti-malarial drugs (Nayyar et al., 2019).While 100,000 children's deaths occur annually due to poor quality

pneumonia treatments (Sample, 2019). Making matters worse pharmaceutical frauds may be harming patients in unforeseen ways. Such as its contribution to antimicrobial resistance (Nayyar et al., 2019). Clearly, pharmaceutical fraud is a critical problem resulting in illness, loss of jobs, and loss of life. A problem only exacerbated when legitimate companies are involved. This topic will be covered through several case studies. But first to gain a deeper understanding of the problem, the next section provides several examples of pharmaceutical frauds. This is followed by the case studies section before concluding.

Examples

The remaining part of this section aims to briefly discuss several examples of pharmaceutical fraud. Let us begin our discussion with a fraud previously mentioned- counterfeiting.

Counterfeiting

As mentioned in the Introduction, counterfeiting has found several definitions. Making matters worse, countries ' legal definitions of what makes a drug counterfeit remain misaligned. Meaning what may be legal in one country is not necessarily legal in another. A cause for concern in a globalized supply chain. Nevertheless, for the sake of this article, we will revert to the WHO's 1999 definition. Which was prompted after 771 reports of counterfeits were reported between 1984-1999. With nearly 78% of these reports coming from developing countries (Deisingh, 2005). Since then, the number of counterfeit incidents have continued to increase in developing countries. Indeed, the WHO estimates that 1 in 10 medical products in low to middle-income countries are counterfeit (WHO, 2019). With the internet playing a key role in the scale-up of counterfeits through means of falsified pharmacies and delivery drug deals (O'Hagan and Garlington, 2018). Counterfeit drugs are a critical issue in more developed countries as well.

In 2016, 1579 North Americans experienced seizures related to taking counterfeit medicine (Acri, 2018). Further, North America is facing an alarming increase of illegally trafficked Fentanyl-laced counterfeits at the time of this writing (DEA, 2020). Fentanyl-laced drugs such as Oxycodone and Xanax add to the growing number of overdoses and deaths related to counterfeit medicine in the illegal drug markets (Castillo, 2021; Moss, 2021; US Department of Justice, 2020). Indeed, counterfeit drugs can be dangerous. Further counterfeits can also be damaging to the drug supply itself.

Beyond breeding an environment of mistrust. Reputations of respectable manufacturers are on the line, as well as brand integrity. Indeed, victims of counterfeit drugs have filed lawsuits against the respectable company for not safeguarding products against tampering (Deisingh, 2005). CAMM's sourced by reputable manufacturers make solving the problem even more difficult. For example, researchers at the University of Kentucky (UK) found that 2 of the 3 companies supplying Acetazolamide to the UK hospital were contaminated and only contained 80-87% of the labeled API amount (Chapin and Willett, 2021). Though the root cause of this issue is still unknown, it may be speculated that the drug product originally contained the labeled amount and degraded over time. If this is the case, a cGMP incompliance may be to blame as these batches of Acetazolamide should have never reached the pharmacy. This leads to the next example-cGMP incompliance.

cGMP incompliance

cGMP is a set of practices designed to ensure quality in pharmaceutical manufacturing (Campbell and Lodder, 2021). GxP extends these practices to x=distribution, clinical, laboratory, and other settings. cGMP and related GxP practices are among the most violated pharmaceutical guidelines (Rovira and Espín, 2009). Though most violations are likely accidental and typically corrected before much harm is done. Not all violations fall under the accidental category. PharmaTech LLC for example, went through numerous inspections and warnings yet still failed to correct cGMP violations (FDA, 2012; Lalama et al., 2016). PharmaTech's inaction allowed for *Burkholderia cepacia (BC)*- an opportunistic pathogen with the capacity to cause serve respiratory illness- growth in the facility's water system (Tavares et al., 2020). The same water was used to formulate the company's over-the-counter (OTC) Dicto Liquid stool softener (Lalama et al., 2016). After infecting several the FDA called for a national recall (Kerr, 2017). Though the damage was done, and PharmaTech would face a lawsuit for the death of a 10-month-old infant. A case that PharmaTech settled in 2020 (Fischer, 2020).

Delaying Generics

Innovator drug companies facing patent expiration may delay generic market entry by suing the generic producers. By claiming allegations that the generic company has infringed on the innovator's patents. Innovators can delay market entry by 30 or more months (Rovira and Espín, 2009). Indeed, the most common delay of generic entry is patent

litigation (Dave et al., 2020). Allowing the innovator to have additional exclusivity on the market that more than compensates for the legal cost of the trials (Feldman, 2017; Rovira and Espín, 2009). Although this tactic is not necessarily fraud, it is an example of gaming the Hatch Waxman Act (Feldman, 2017) and is estimated to be costing Medicaid millions (Dave et al., 2020). Additional methods for delaying generics include refusal of product samples, which are needed to prove bioequivalence (Feldman, 2017).

Price Hikes

Between 2009 to 2016, Mylan raised EpiPen prices by more than 400% (Carrier and Minniti, 2017). Resulting in the epinephrine delivering device costing over $600. When the medicine itself only cost pennies per dose (Carrier and Minniti, 2017; Glabau, 2017). Further, Mylan misclassified EpiPen as a generic instead of a branded drug. Resulting in Mylan paying lower rebates to the government (SEC, 2019). In essence, withholding millions of rightly owed funds from Medicaid. Mylan settled the violation against the False Claims Act by agreeing to pay $465 million (US Department of Justice, 2017). Additionally, Mylan refused to work with government investigators throughout the investigation process. Specifically failing to disclose or accrue for losses relating to the investigation (SEC, 2019). This time Mylan agreed to pay $30 million to settle the disclosure and accounting failures (SEC, 2019). Mylan's EpiPen prices are not necessarily fraudulent; but they are arguably unethical as they limit access to lifesaving medicine. Other examples of price hiking are Daraprim's 5000 percent increase by then Turing Pharmaceuticals (Luthra, 2018) and Novartis' one-time injection for spinal muscular atrophy that costs $2.1 million, Zolgensma (Lupkin, 2019). Even insulin has been targeted with manufacturers facing recent lawsuits over alleged price fixing (Anderson, 2020; Sagonowsky, 2019).

2 METHODS

The potential for monetary gain through unethical or fraudulent acts is examined in four case studies. These studies focus on legitimate companies that opted a dishonest path. The studies include - purchasing and distributing from unlicensed sellers, unlawful promotion of Paxil, Wellbutrin, and Avandia, and concealing knowledge of cancerous risk data. Financial and economic information is gathered through mining the US Department of Labor Statistics, govinfo, US Securities and Exchange Commission, and US Department of Justice databases.

3 RESULTS

CAMM are a serious threat to the pharmaceutical supply chain as they are difficult to detect and can by life threatening. CAMMs become an even larger threat when they are sourced through reputable companies. To shine light on this topic and provide an understanding of the problem and its respective monetary motivates this section examines the economics and potential monetary gain surrounding four cases of pharmaceutical fraud. Examined cases included-purchasing and distributing from unlicensed sellers, unlawful promotion of Paxil, Wellbutrin, and Avandia, and concealing knowledge of cancerous risk data. For each case, an economic screenshot is provided which summarizes potential pressures, motivates, and goings-on during the time of the event.

Purchasing and distributing from Unlicensed Sellers

A unique scheme was developed by Cumberland Dis- tribution, Inc., ("Cumberland") a wholesale prescription drug distributor licensed in Tennessee (TN). The company knowingly bought prescription drugs from unlicensed "street sellers" (Middle District of Tennessee, 2013). Purchasing took place in New York and Miami through a network of individuals with legitimate prescriptions. Drugs entangled in this scheme include drugs used to treat immunodeficiency virus/ acquired immunodeficiency syndrome, antipsychotic, antidepressants, blood pressure, and diabetes (Middle District of Tennessee, 2013; Roth, 2021a). The drugs were then shipped to Cumberland's warehouse located in Nashville, TN. Here the drugs underwent cleaning, organizing and repacking before being sold and distributed to independent pharmacies. Those involved attempted to evade authorities by setting up private emails, purchasing burner phones, and renting another warehouse (Boling, 2018a). Red flags surrounding the Cumberland case included a number of reports claiming drug bottles contained the wrong medicine, incorrect labeling, and foreign objects. Several reports claimed at least one bottle contained tic tacs instead of medicine (Boling, 2018b).

The Cumberland's economic screenshot surrounding this case is:

- The crimes took place between December 2006 to August 2009 (Middle District of Tennessee, 2013) in Nashville, TN; Miami, Florida; and New York, New

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York. During this time the US was facing an economic recession in which over 8 million jobs were lost (Barello, 2014). This may have given individuals an incentive to sell their drugs cheaply for extra cash. However, some studies suggest American's Pharmaceutical sales went up nearly 12% during the recession.

- Unemployment rates peaked around 10% (Cunningham, 2018).
- Pharmaceutical companies conducted large scale lay-offs. For example, Pfizer laid off over 1,000 employees in 2009 (Buxton, 2019).
- Raw material import costs increased (Buysse, 2010).

The scheme resulted in the company grossing over $50 million-dollar in proceeds. Resulting in over $14 million dollars in profit. Criminal charges were brought against the company's President and two co-workers. Cumberland's President was found guilty of Mail Fraud. The president was made to forfeit $1.4 million and was sentenced to six years in prison. Further, the court order for restitution payments totaling $3,386.08 to two pharmaceutical companies (Middle District of Tennessee, 2013).

Unlawful Promotion of Paxil, and Wellbutrin, and Avandia

In 2012, GlaxoSmithKline (GSK) pleaded guilty and agreed to the largest pharmaceutical fraud settlement in US history at the time (Office of Public Affairs, 2012). The settlement was a result of GSK's unlawful promotion of Paxil, and Wellbutrin. Along with the failure to disclose clinical safety data of the diabetes drug Avandia (District of Massachusetts, 2012). Court documents reveal claims that between January 1, 1998, to December 31, 2003, GSK promoted off-label uses of Paxil. Between January 1, 1999, to December 31, 2003, GSK knowingly promoted Wellbutrin for off- label uses (e.g., weight loss and sexual dysfunction) and at dosages other than those for which it was approved by the FDA (Ortiz, 2012). Further claims made in the settlement involved the asthma medication Advair being unlawfully promoted between January 1, 2001, to June 30, 2010, concerning dose. Lamictal between January 1, 1999, to December 31, 2003, being promoted off-label. Zofran between January 1, 2002, to December 31, 2004, being promoted off-label. And a kickback scheme involving Praxil, Wellbutrin, Advair, Imitrex, Lotronex, Flovent and Valtrex (Ortiz, 2012).

Focusing solely on Paxil, Wellbutrin, and Avandia, the economic gain of GSK's actions was enormous. Though difficult to separate the "honest" profit from dishonest profit, one can gain an idea from looking at the sales during the years covered by the settlement and the fine given. Here is a screenshot of GSK sales during the settlement period.

- Paxil brought in $11.6 billion in sales.
- Wellbutrin brought in $5.9 billion in sales.
- Avandia brought in $10.4 billion in sales (Sifferlin, 2012).
- GSK agreed payout is as follows.
- GSK agreed to pay $1 billion in criminal penalties. The $1 billion criminal fine was broken down as follows.
    - $159,768,000 for the unlawful promotion of Paxil.
    - $554,433,600 for the unlawful promotion of Wellbutrin.
    - $43,185,600 criminal forfeiture for Paxil and Wellbutrin.
    - $242,612,800 criminal fine for Avandia.
- GSK agreed to pay $2 billion in civil damages to federal and state healthcare programs. The $2 billion dollar fine for civil damages was broken down as follows.
    - Federal Recovery: $1,501,618,568.
    - State and Public Health Service (PHS) recovery: $498,381,432 (Ortiz, 2012; US Department of Justice, 2012).
- The GSK'S economic screenshot between 1997 to 2010 is:
- Zantac's market exclusivity was terminated in July 1997 (Bendt et al., 2002
-). Until this date Zantac was bringing in the Glaxo Wellcome company nearly $1.6 billion in U.S revenue annually (Moore, 1997).
- Asian financial crisis began in 1997.
- The early 2000s recession covered approximately 1 year of the settlement range. Further, this recession was noted for its general decline in exports. Along with a decline in businesses investing in structures and inventories (Kliesen, 2003).
- The US was facing the great recession in approximately 2 (2007-2009) of the ~10-12 years (1998-2010) covered by the case (Barello, 2014) .This event may have contributed to the ~£1 billion

drop in pharmaceutical US sales and subsequent drop in profit in 2007 (See Figure 1 and 2).

- Augmentin lost patent protection early in 2002 with the patent meant to last until 2018. Augmentin was GSK's second largest drug in the year prior (Tesler, 2004).
- Avandia lost market exclusivity in 2008.
- Avandia experienced regulatory whiplash. In 2008, the FDA mandated the medicine come with black box label concerning increased ischemic cardiovascular risk. This was later retracted in 2010. There is some evidence that this may have influenced patients taking it and hence sales (Hickson et al., 2019).
- Advair lost market exclusivity in 2010. However, the FDA did not approve the first generic of Advair until 2019 (Meyer, 2019).

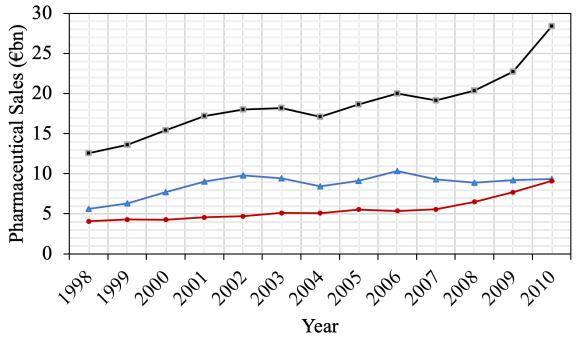

Figure. 1. Summarizes GSK's total pharmaceutical sales (black line), US pharmaceutical sales (blue line), and European pharmaceutical sales (red line) between 1998-2010. Data gathered from GSK's annual in- vestor reports(GSK, 2010, 2009,, 2008, 2007, 2006, 2005, 2004, 2003, 2002, 2001, 2000).

GSK faced numerous patent expiration and multiple economic recessions during the time covered in the $3 billion settlement. GSK also suffered multiple negative results in clinical trials with drugs such as Praxil, lack of efficacy for depression in patients under the age of 18 (Office of Public Affairs, 2012). Further, generic introduction can cut nearly 90% of a company's sales (DeRuiter, 2012). The numerous losses of high-profit drugs during a short time with multiple recessions and negative clinical results may have incentivized the company's dishonest actions. Nevertheless, the scheme was brought to light by whistleblowers. Notably Thomas Gerahty, a former senior marketing development manager for GSK, and Matthew Burke, a former regional vice president for GSK (Kelton and Brown, 2011; Phillips & Cohen, 2012).

Concealing cancerous risk of pioglitazone

In 2015, Takeda Pharmaceutical agreed to pay a product liability settlement of $2.37 billion (Casseres et al., 2020). The settlement came approximately a year after Takeda and partner Eli Lilly were ordered to pay $9 billion (75% paid by Takeda and 25% paid by Lilly) for concealing knowledge of pioglitazone (brand name Actos) bladder cancer risks. Though the $9 billion quickly dwarfed to $36.8 million after appeals (Grisham and Harding, 2015). Both cases originate from a 2011 lawsuit against Takeda by Terrence Allen and Susan Allen. The allegations against Takeda were that Actos had caused Terrence's bladder cancer. However, Takeda argued that "bladder cancer *cannot* occur within one year of exposure to a causative agent" (Doherty, 2014). Despite this, the jury awarded $1.475 million in compensation to the Allens (Doherty and Magistrate Judge Hanna, 2014). Although the Allens were not the first to accuse Takeda of concealing knowledge they were the first to be successful in court (Sullivan, 2018). Following the Allens' success, numerous lawsuits against Takeda with similar allegations cropped up. Ultimately leading Takeda to its $2.37 billion settlement agreement. Despite the settlement, multiple studies have continued to conflict with the court's decision that Actos is associated with increased rates of bladder cancer (Lewis et al., 2015; Tang et al., 2018). Nevertheless, the FDA backs the position that pioglitazone does have the potential for cancerous risks (FDA, 2011b).

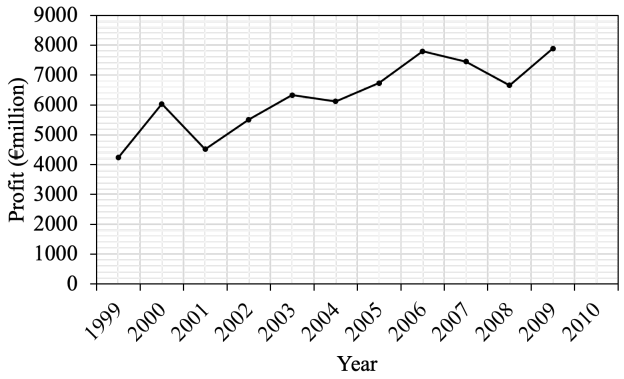

Figure. 2. Summarizes GSK's profit before taxation by year. Data gathered from GSK's annual investor reports (GSK, 2010, 2009, 2008, 2007, 2006, 2005, 2004, 2003, 2002, 2001, 2000).

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In addition to potential bladder cancer risks, Actos also carries a black-boxed warning. Stating the users of Actos are at an increased risk of congestive heart failure. The warning came alongside Avandia's black box warning in 2007 (Tanne, 2007) .Unlike Avandia, Actos black-box label stuck. To gain a deeper understanding of Takeda during this time, let us look at an economic screenshot.

The economic screenshot of Takeda's early years to roughly 2011 is:

- 1985 Takeda began globalizing via a joint venture with Abbott Laboratories through TAP Pharmaceuticals.
- 1985 TAP begins marketing Lupron.
- 1989 TAP releases Lupron Depot.
- 1991 Lansoprazole proton pump inhibitor launches in Europe.
- 1995 Lansoprazole (brand name Prevacid) approved in the US.
- Between 1995-1999 Takeda launched several worldwide ventures including
    - Established Takeda UK in 1997.
    - Established Takeda Ireland in 1997.
    - Established a R&D and holdings group in America in 1997.
    - Established Takeda America in 1998.
    - Established a European R&D center in 1998 (Takeda, 2021).
- Actos gained FDA approval in 1999.
- In 2001, TAP agreed to pay $875 million for unlawful promotion of Lupron. This was one of the earlier settlements against the False Claims Act in the US (Girard, 2009).
- According to court documents Actos net sales between 1999 and 2012 were $24 billion dollars (Doherty, 2014).
- Novartis and TAP came to a licensing agreement for Prevacid in 2005 (Japsen, 2005).
- Actos was the world's top selling diabetes drug in 2007. This may have resulted from rival drug Avandia's link to heart attacks during the same time (Turner et al., 2021).
- Novartis gained Prevacid OTC approval by the FDA in 2009 (Novartis, 2010).
- Actos sales peaked at $3 billion in 2010 (Doherty, 2014).
- In 2011. Germany and France pulled Actos off the market (Turner et al., 2021).

From the economic screenshot above, it seems that Actos launched around the time Takeda was expanding. As an up and coming company attempting to globalize, it would seem natural to expect pressures for blockbuster developments such as Actos to exist within the company. Assuming Takeda was aware of the potential risks of Actos. The company may have been incentivized to conceal this knowledge due to the company undergoing a critical stage in its development.

4 DISCUSSION

The three case studies above provide context of the links between monetary incentives and fraudulent acts. Such behavior has contributed to the industry's past reputation for holding stakeholder opinions over patients (Kessel, 2014). Though recently, the industry has had an improvement in reputation. The 2019 PatientView survey showed that 46% of patients surveyed viewed pharmaceutical companies as excellent or good- a 5% increase from the year before (Wyke, 2020). Even generic companies saw an increase in reputation from 34 to 35% (Wyke, 2020). But with nearly continuous unethical behavior being uncovered through the FDA and independent investigators such as Valisure and UK's Quality Study, will an improved reputation hold? It would seem difficult as bad actors continue to target vital materials. Lacking quality controls with Remdesivir processing (Almeter et al., 2021), counterfeited COVID-19 vaccines (FDA, 2021), and contaminated hand sanitizer with Benzene (Henderson, 2021) are just a few examples. It would not be surprising for the entire healthcare sector to take a hit in reputation with such acts. So comes the question- how do we combat pharmaceutical fraud?

Many argue that in order to combat pharmaceutical fraud, the penalty must be placed on corporate executives, and it must be higher than the company simply writing a check. Instead, criminal charges directly against CEOs and executives resulting in prison sentences are suggested (Waters, 2012). However, in the US, it is challenging to convict company executives of pharmaceutical frauds. Even the infamous former CEO of then Turing Pharmaceuticals, Martin Shkreli (aka Pharma bro) was found guilty of security frauds not necessarily pharmaceutical frauds (Gizzi and Schmidt, 2017). Despite his alleged involvement with Daraprim's ongoing 5000% price hike (Siddons, 2021). Conviction for pharmaceutical fraud is not impossible though.

Insys Therapeutics founder John Kapoor and several

executives were found guilty of illegal distribution of a controlled substance (Dyer, 2019). The case made history as the first time prosecutors had brought criminal Racketeer Influenced, and Corrupt Organizations (RICO) charges against pharmaceutical executives (Ortyl, 2019). The conviction sentenced John Kapoor to 66 months in the custody of the Bureau of Prisons, followed by three years of supervised release (Massachusetts, 2020). Executives involved faced lesser time with the minimum possible prison time given to Michael L. Babich, the former CEO of 2 months, but it could be as much as 30 months (Massachusetts, 2020). Additionally, the FDA took action against members involved. Permanently debarring former Insys executive Sunrise Lee from "providing services in any capacity to a person that has an approved or pending drug product application" (Roth, 2021b). Similar debarment notices were given to others convicted, including John Kapoor (Roth, 2021c, 2020a, 2020b). Indeed it seems that Kapoor's potential for future monetary incentives to commit fraud was stripped. However, it is yet to be seen if such punishments will decrease corporate pharmaceutical frauds.

5 CONCLUSION

Several common examples of pharmaceutical fraud have been presented. Including counterfeiting, cGMP incompliance, and more. In addition, case studies have been explored. Though each example and case studies vary in detail, they all stay linked through the monetary incentives for the actor. Assuming the companies involved in the case studies were not caught, they would have made off with billions of unjustly earned money. Findings suggest that monetary incentives are common among unethical fraud cases. Economic recessions, patent expirations, and company expansion are amongst the most consistent economic factors surrounding the cases studied. Suggesting these variables may be predictors of potential drug quality issues.

It will be interesting to see how the industry's reputation holds up as more independent investigators join the FDA in the fight against pharmaceutical crimes. As more and more cases are uncovered, it seems there is a vital need for reform, whether in policy or punishment. Otherwise, we can expect more pharmaceutical fraud in our daily news headlines.

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