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TREATING AMERICA: AN ANALYSIS OF PHARMACOLOGICAL ECONOMICS

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ABSTRACT

Healthcare is a big business, plain and simple. Hospitals, clinics and healthcare providers "sell" their services to consumers. In most business models, competition between businesses typically drives costs down, allowing for the consumer to benefit. However, this is not the case when it comes to healthcare costs within the United States. Costs are at an all-time high with no signs of slowing down. When the top 5% of Americans earners account for nearly half of all healthcare spending because they are the only ones with the means to afford it, it raises alarm. In per capita spending, Americans spend anywhere from $4,000-$6,000 more than citizens in 30+ industrialized countries including Canada, Germany and the United Kingdom; it is time to diagnose the cause of our higher costs (OECD, 2017). This scenario was ultimately caused by complacency and a lack of health education about the current U.S. healthcare system. One of the key contributors to rising healthcare costs is the development, production, and distribution of pharmaceutical products. When key elements of the U.S. healthcare system are allowed to go unchallenged, without evaluation, or encouragement to evolve to meet changing needs; costs are then allowed to grow rampant without any oversight.

KEYWORDS: Pharmaceutical Industry, Healthcare, U.S. healthcare.

INTRODUCTION

Healthcare is a business, plain and simple. Hospitals, clinics and healthcare providers "sell" their services to consumers. In most business models, competition between businesses typically drives costs down, allowing for the consumer to benefit. However, this is not the case when it comes to healthcare costs within the United States. Costs are at an all time high with no signs of slowing down. When the top 5% of Americans account for nearly half of all healthcare spending because they are the only ones with the means to afford it, it raises alarm ("How Health Expenditures Vary across the Population.," N.d.). Americans spend anywhere from $4,000-$6,000 per capita[1] more than citizens in countries like Canada, Germany and the United Kingdom; it is time to diagnose the cause of our higher costs (OECD, 2017). The cost inflation for American consumer pharmacological products is created by the healthcare industry profit maximization efforts. Big pharmacology companies play on the compliancy and a lack of education about the current U.S. healthcare system by the average consumer and wield their influence through media campaign efforts, and direct lobbying efforts to influence health care regulations and laws. When the U.S. healthcare system is not continuously challenged and allowed to serve profit maximization unchecked, costs grow rampantly without effective pricing oversight nor the competitive marketplace forces that generally drive cost down and quality up.

Overview of the American Healthcare System

We have known that healthcare costs have been on the incline for some time. From just over $4,500 per capita in healthcare expenditures in 2000 to just shy of $9,500 in 2015, the steady rise of costs has been great cause for alarm, shown in figure 1. Americans pay more for their healthcare compared to any other industrialized nation in the world. What is troubling is that Americans not only out spend every nation in the private sector[2], but they also out spend almost every industrialized nation in the public sector[3] as well, shown in figures 2-4. This vast contrast in healthcare expenditure per capita showcases that the United States' healthcare system is not economically efficient nor sustainable without negatively influencing both consumers and the government. In addition, the United States is outpaced, in terms of cost, by nations with comparable healthcare systems. These nations, like Japan, Germany, the United Kingdom, Switzerland, Canada, etc., who are similar or even supersede the United States in life expectancy and infant mortality rates; annually undercut, by thousands of dollars, the per capita expenditure of the US's healthcare system.

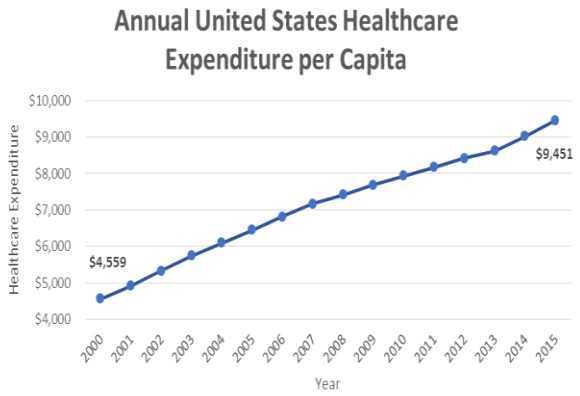

Figure 1: Taken from OECD Health Report stat, accounts for all healthcare expenditures, public or private in the United States.

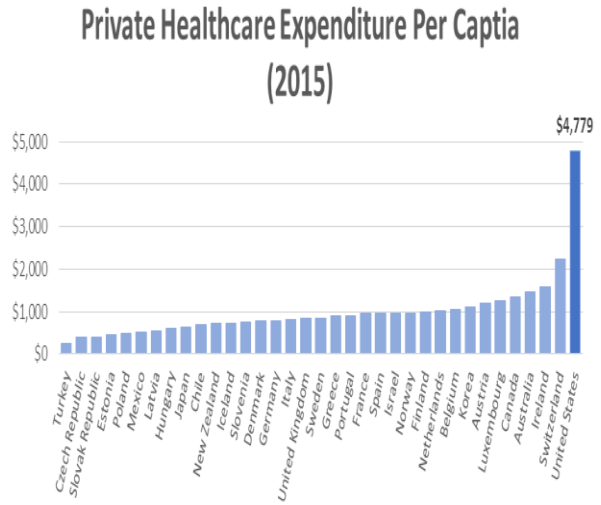

Figure 2: Taken from OECD Health report stat, accounts for all private healthcare expenditures in OECD reporting countries. Prices use current Purchasing-Power-Parity to the US dollar.

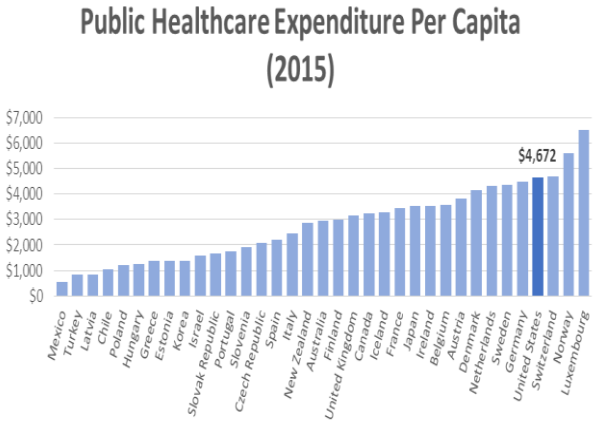

Figure 3: Taken from OECD Health report stat, accounts for all public healthcare expenditures in OECD reporting countries. Prices use current Purchasing-Power-Parity to the US dollar.

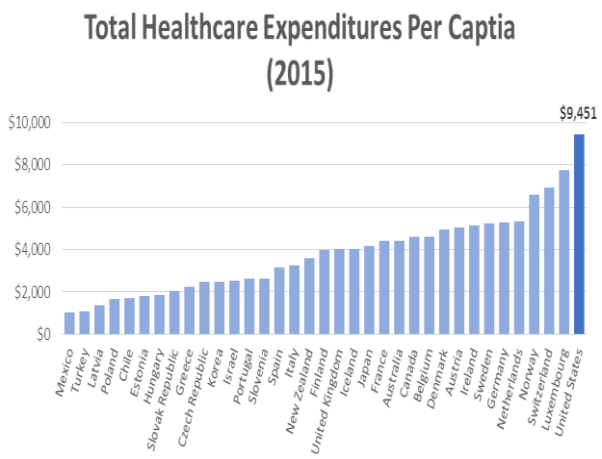

Figure 4: Taken from OECD Health report stat, accounts for all healthcare expenditures, public and private, in OECD reporting countries. Prices use current Purchasing-Power-Parity to the US dollar.

The Role of the Pharmaceutical Industry

Several facets of the US healthcare system has come under scrutiny in recent years. From one of the largest bills passed in congress on US healthcare since Medicare and Medicaid, the Affordable Care Act, to its potential repeal and replacement under the Trump administration, US healthcare has been a topic of much heated debate. However, even with the new regulations on insurance companies to hospital reimbursements, there has been one industry that has gone almost seemingly untouched. The pharmaceutical industry has been allowed to carry on with its status quo with near monopoly pricing without effective oversight or controls in place. In order for the industry to evolve to meet consumers' needs for fairly priced treatment options, it must be challenged and evaluated before it is allowed to grow rampant. In the latest OECD report, pharmaceutical spending amounted to $1,112 per capita in 2014, a 44% increase over the next highest spending country, (figure 5) (OECD, 2017).

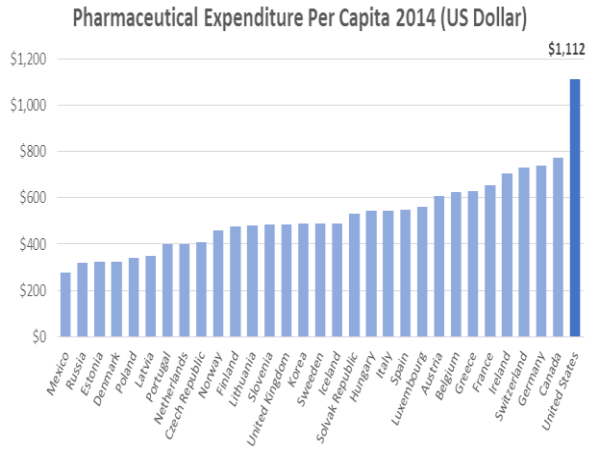

Figure 5: Taken from 2014 OECD Health report stat, accounts for final expenditure on pharmaceutical products. Prices use 2014 Purchasing-Power-Parity to the US dollar.

Unlike other facets of healthcare, the pharmaceutical industry is an outlier in terms of its financial structure. Whereas other parts of healthcare can vary from being public to private entities depending on the healthcare model, pharmaceutical corporations are almost entirely private entities. The simple truth is that they do not innovate purely out of charity; these corporations are profit driven and must meet demands of shareholders or risk closing their doors. Like a typical corporation in the United States, they pay executives, invest in future innovations, and advertise their products, all of which adds to the inherent cost to manufacture pharmaceutical products. Developing innovative, cutting edge pharmaceutical drugs is not cheap nor without heavy risks. Many new drug trials/products fail prior to ever reaching Phase III testing let alone Food and Drug Administration (FDA) approval and can cost millions in development costs.

When evaluating the public annual financial reports of 10 different corporations from the years 2003-2015 a trend emerges. In several of the corporations, the United States accounted for a significant portion, sometimes over 50% of the total revenue from pharmaceutical products. In Figure 6, the total revenue accumulated for each corporation from 2003-2015 is demonstrated as a proportion between the contributions of United States and the rest of the world. Revenues were taken from annual financial reports from each corporation with corrections.[4] The proportions showcase the greater contribution that the United States healthcare system accounts for with each of these corporations.

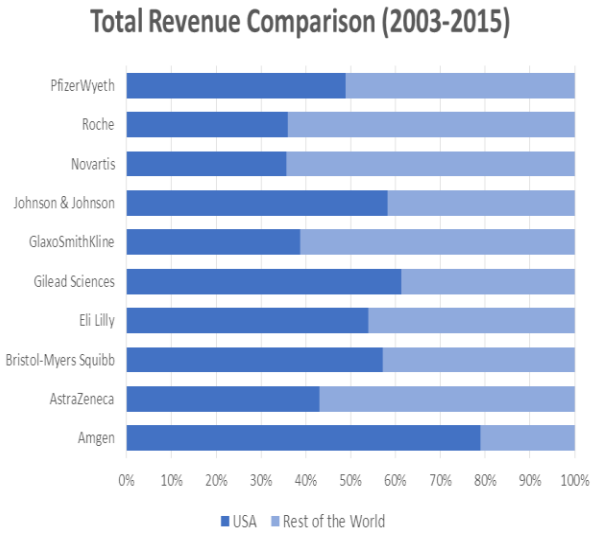

Figure 6: Figure was derived from public financial reports from each corporation represented. The Figure represents the total revenue from 2003-2015 of each corporation. Pfizer Wyeth uses the combined total revenues of Pfizer and Wyeth before their merger in 2009.

This symptom of increased expenditure on pharmaceutical products is not the direct result of an increased consumption of such products; rather, it can be attributed to an increased cost of the products themselves. The International Federation of Health Plans (IFHP) released a report in 2015 showcasing the disparity in prices between the US and other nations in terms of pharmaceutical products. Several benchmark drugs were utilized in the study and the results were disconcerting, (Figure 7). A wide variety of drugs were presented, with the United States topping the charts for each benchmark drug, sometimes by thousands of dollars in difference compared to other countries.

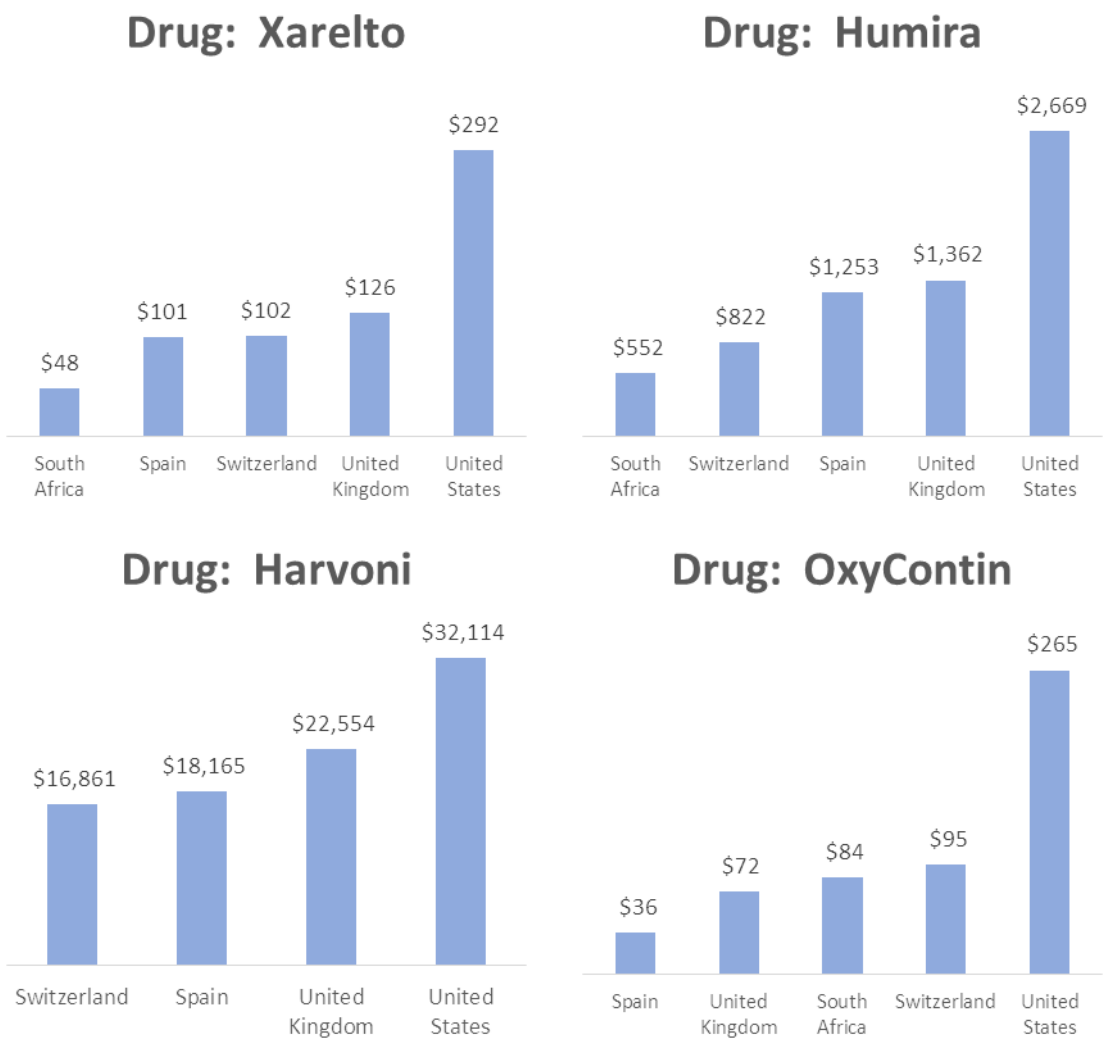

Figure 7: Taken from IFHP 2015 report using average cost of prescription in each country. Based off US dollar. Xarelto is used to prevent or treat blood clots; stats are based off of 30 capsules, 20 mg, 30 day supply. Humira is used to treat rheumatoid arthritis; stats are based off 1 prefilled syringe carton, 2 syringes, 28 day supply. Harvoni is used to treat hepatitis C; stats are based off 28 tablets, 4-week supply. Oxy Contin is used to treat severe ongoing pain; stats are based off 60 tablets, 20 mg, 30+ day supply.

The disparity in price difference between the United States and the rest of the world in the cost of pharmaceutical products is apparent. Several factors can be attributed to the price difference; however, the majority of factors can be stripped down to one simple argument: regulation. When comparing the United States' healthcare system to that of other nations, it becomes clear that the United States is not as efficient or effective with its regulations on the pharmaceutical industry. Outside the United States, the costs that a drug can be sold for is often highly regulated by that country's health care agency, which sets price controls that allow for moderation in both cost for the patient and revenue for the drug manufacturer. Several deficiencies of US regulations can be attributed to adding cost to the drugs that everyday Americans utilize. From inefficiencies in the FDA to lack of price control regulations, all contribute to the elevated cost on drugs in the United States.

The Cost of Developing Life Saving Treatment

Several major contributors lead to the high expenses of life-saving treatments; one of which is the cost of research. The road for researching treatments and procedures that have the capability of saving lives is a very long one. It can take years, even decades, to research these treatments. At a price tag of at least $3 billion for a Food and Drug Administration (FDA) approved drug and going upwards of $11 billion (Herper, 2012), researching different treatments has an exuberant price tag. The cost of research and development of 12 pharmaceutical companies compared to how many drugs were approved in a 15-year time span can be seen in Figure 8 and Figure 9. This cost of research drives up the price that the average consumer must pay for treatment.

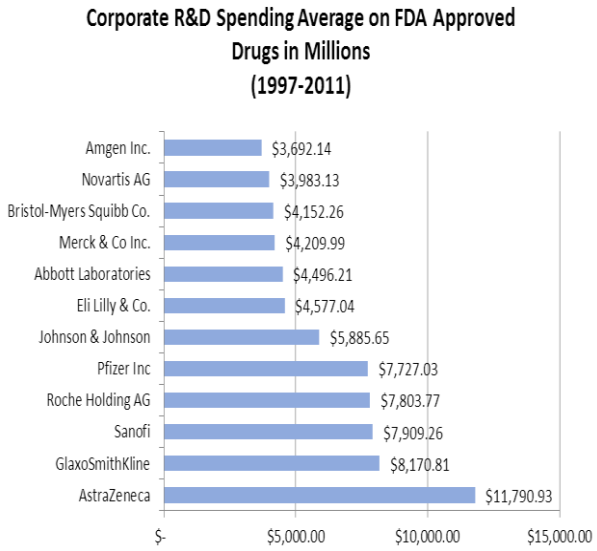

Figure 8: Average research and development spending on FDA approved drugs in millions of dollars for 12 pharmaceutical companies in a 15 year time span from 1997 to 2011. Averages were calculated from total amount of money spent on research and development from years 1997 to 2011 and divided by the amount of successful drugs produced within those years (Herper, 2012).

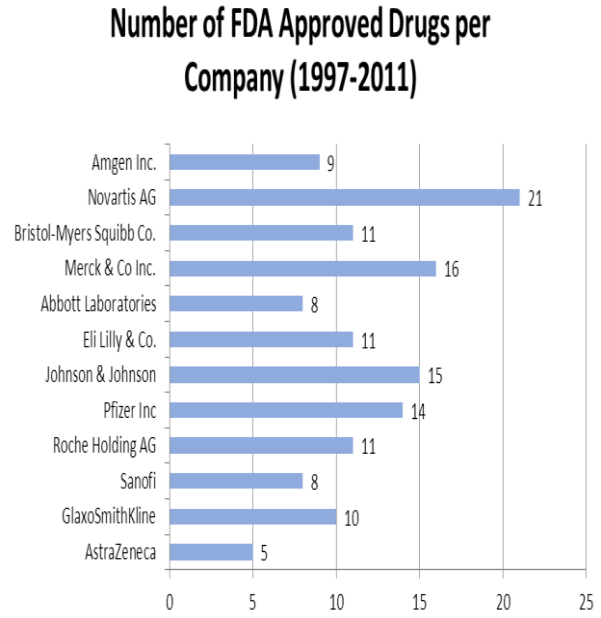

Figure 9: Number of FDA approved drugs from 12 companies from the years 1997 to 2011 (Herper, 2012).

Estimated vs. Actual Cost of Research.

To research and develop a brand new drug, pharmaceutical companies have long preached that the average cost has been roughly one billion dollars (Light). Accounting for general inflation, this has now been inflated to $1.32 billion. This statistic comes from a 2003 study published in the *Journal of Health Economists* by economists Joseph DiMasi, Ronald W. Hansen and Henry Grabowski; however this staggering statistic is grossly overestimated. A compelling new study by Donald Light and Rebecca Warburton (2011) has shed new light on the highly skewed 2003 study. Light and Warburton have been able to estimate the cost of research and development of a new drug to just $55 million. This calculation has been performed by accounting for errors in the 2003 study. For instance, the 2003 study does not account for all of the tax breaks that pharmaceutical companies receive on research and development of new drugs.

Unlike any other long-term investment that is depreciated gradually over time, research and development costs come directly from gross profits, creating an instant 100% tax deduction from profits of pharmaceutical companies saving them millions, if not billions of dollars a year (*Economic Recovery Tax Act of 1981*, 1981; Light and Warburton, 2011).

The more expensive research and development of a drug costs pharmaceutical companies, the greater the tax break they receive. Additionally the original study used the average cost (mean[5]) instead of the median[6] cost which Light and Warburton argue, is misleading, because research and development costs for different drug products vary widely, and a few expensive drugs can and will grossly skew the mean cost of research and development. Due to outliers in a data set, using mean as an interpretation of statistical data can give a false representation of the data. Using median as an interpretation of the data in this case is a better alternative because of its ability to show where the bulk of the distribution of data lies, prohibiting outliers from skewing the data. This happened in the original study when the 2003 study's median was 74 percent of the mean, meaning that the bulk of the distributions of costs of pharmaceutical drugs were skewed by a few outliers in the data. By accounting for all of these errors, Light and Warburton have estimated the cost of research and development of an approved drug to be an average of $75 million and a median of $55 million.

This means according to the Light and Warburton study, that the pharmaceutical companies' average of $1.32 billion is off by $1.265 billion.

With research and development of an approved drug only topping out at $55 million, what accounts for the other $2.945 billion out of the $3 billion minimum spent for FDA approved drug development? The unfortunate reality is that the $2.945 billion unaccounted for is spent on failed research. Currently fewer than 1 in 10 drugs are actually successful in clinical trials (Herper, 2012). The reality of modern day research is an ugly picture. Pharmaceutical companies will often times withdraw drugs from clinical studies on their own accord. This happens often when companies feel as though a particular drug will not make enough money in order to meet the high threshold of cost of research and

development. This ultimately wastes millions of dollars on research when corporations' choose economical gain over the potential benefits of a new drug. In addition, failed research can also occur when pharmaceutical companies attempt to improve upon medications that are already available on the market. This occurs when a proposed new drug cannot demonstrate a significant enough of a statistical improvement upon an already existing drug. These drugs often make it to the final stages of clinical trials and once they cannot demonstrate a marked improvement, the FDA will, many times, dismiss the proposal all together. When proposed drugs do not pan out, either from not meeting expectations, not being able to make the high threshold of cost in order to be profitable, or not improving upon drugs already on the market, the failed research becomes the biggest cost for research and development of approved drugs and grossly outweighs the actual cost of developing a new drug.

Creating Demand – Media's Influence on Drug Sales

Advertising of prescription treatments raises both the cost of developing a new drug as well as the cost of healthcare due to pharmaceutical companies trying to recuperate their costs. In America, pharmaceutical companies advertise their product not only to physicians but also to patients; the majority of these treatments that are advertised cannot be done without the written prescription from a legal practicing physician. This means that millions of dollars each year are spent by pharmaceutical companies on advertising to individuals who cannot make use of these treatments without the consent of highly educated professionals, professionals whose entire profession is based off providing the best treatment options for patients.

In many cases, the amount of money spent on advertising pharmaceutical products far surpasses the amount of money spent on the actual research and development of the products to begin with. This becomes noticeable with looking through the annual financial reports of 10 leading pharmaceutical corporations from the years 2003-2015 (Figure 10).

An extreme example of this is Astra Zeneca where 38% of their total revenue from 2003-2015 was allocated strictly to marketing of their products compared to just 17% spent on research and development. Of the 10 corporations evaluated, only Gilead Sciences allocated more revenue to research than marketing at a 2% difference. However, The 15% allocated to research by Gilead Sciences paled in comparison to the 40% pure profit.

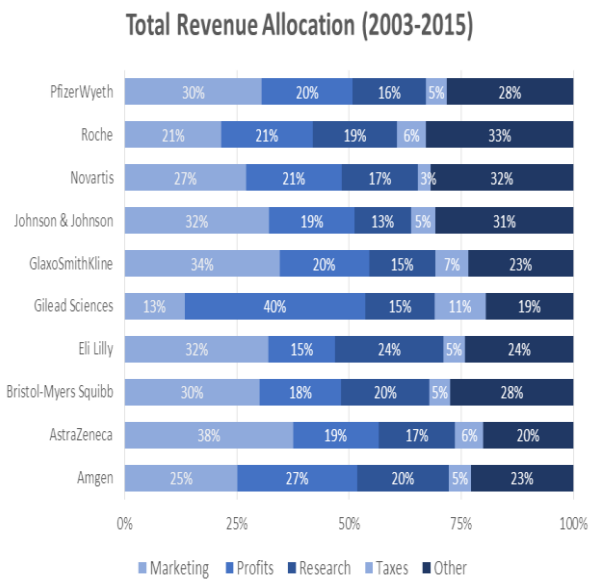

Figure 10: Total revenue allocation by category of 10 pharmaceutical corporations. Data was derived from the annual financial reports from each corporation from 2003-2015. Data used was the total revenue allocations from 2003-2015 summed together. Pfizer Wyeth uses the combined allocations of Pfizer and Wyeth before their merger in 2009.

The average American consumer wants to feel informed and in control of their ailment. The most common practice of any individual who has just been diagnosed with a major disease is to search for any information that they can find about their condition. Some may argue that by advertising prescription medications to consumers, they will inform the general population about different medical conditions. The idea is that individuals who have lived with a condition all of their life may find out that they no longer need to suffer with their ailment, due to a medication currently on the market. However, this is a poor approach to trying to inform and treat the general population. This is due to the fact that most direct-to-consumer advertising is not informative about the medical condition itself, but rather tries to sell a product. When observing any general prescription medication advertisement, often times the actors or "testimonies" exclaim that they are much happier while on the advertised medication. The medication is often shown to empower the individuals in the advertisement without presenting any compelling information about the actual disease itself. This vague information can lead to individuals believing that they might have diseases they do not due to them trying to self-diagnosis their condition. This self-diagnosis can then lead to patients pressuring physicians to prescribe medication to them that they do not need. It is by no mistake that the media (commercials, web pop ups, etc,) are intended to show the miracle drug that will change a person's life no matter what the condition or underlying ailment.

The business model of advertising prescription medication to patients in the United States is unlike the European model where advertising treatments to patients is illegal as dictated by the European Union (European Union, 2001). For every dollar spent on developing a new drug, on average, $1.57 is spent on advertising. From 1997-2005 spending on research and development has increased on average, 9.3% for a total of 103.3% over 8 years (Figure 11) (*Prescription drugs: improvements needed in FDA's oversight of direct-to-consumer advertising: report to congressional requesters*, 2006). Compared to total advertising, spending has increased on average 11.12% for a total of 128% increase over 8 years. What's more alarming is the percent increase on advertising spending to physicians compared to direct-to-consumer (DTC). On average, physician advertising spending has increased just 8.3% for a total of an 85% increase over 8 years, in comparison to the average of Direct-to-Consumer advertising spending which has increased 19.1% a year for a total of 282% over 8 years. The constant increase of the spending allocated to Direct-To-Consumer advertising drastically increases the cost of developing a new treatment thus necessitating a high ticket price for the treatment passing on the high cost onto the patient. Creating consumer demand for a drug without fully understanding the side effects, risks and other considerations is dangerous as people often demand a drug in the doctor's office without a proper assessment or the most effective treatment option.

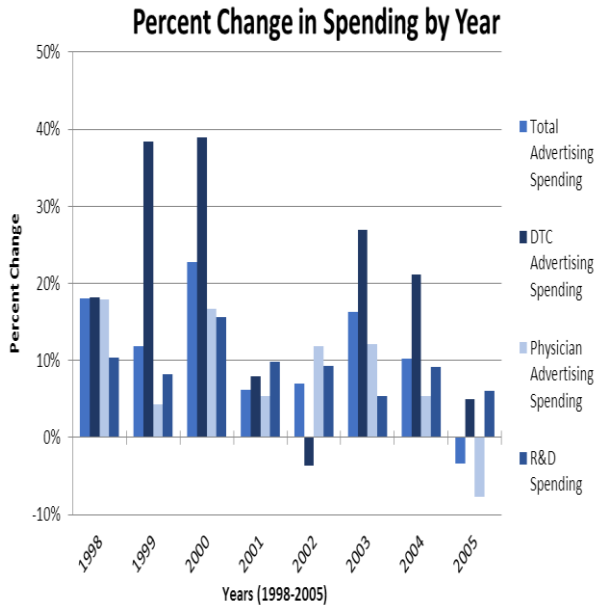

Figure 11: Percent Change in Spending by year from the years 1998-2005. This graph compares total advertising spending, Direct-To-Consumer advertising spending, physician advertising spending, and research and development spending ("Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising").

Regulating the Market Place

The Food and Drug Administration and the Politics of Approving Drugs.

The other part of researching a new drug is the actual approving process by the Food and Drug Administration (FDA). The FDA was established by President Theodore Roosevelt in 1906 for the purpose of approving products that Americans consume each and every year relatively safe[7] for human consumption. The FDA's process for approving safe treatments for patients is long and costly. It can take years for a drug to be deemed safe for human consumption and can cost pharmaceutical companies millions of dollars. Pharmaceutical companies pass those costs onto the consumer, in the hopes of being able to market a new drug. The typical drug approval process endures several phases of evaluation including: animal testing, multiple human trial groups, several panel reviews, and multiple research papers deeming the drug safe. This lengthy process is a major contributor to the cost of developing and researching new drugs and the rising costs of healthcare overall.

The process of receiving approval from the FDA for the marketing and distribution of a new drug begins long before the FDA even becomes involved. Several studies must take place before a drug can be deemed safe for human clinical trials. This can take years of research outlining the intended effects of the drug, production methods, and the overall interactions the drug has with the human body on a molecular scale. These tests are traditionally concluded with tests performed on animals similar to humans[8] in order to validate that the drugs are indeed safe to move to human trials.

Once these tests have concluded, pharmaceutical companies will submit what is called an Investigational New Drug (IND) application to the FDA. According to the FDA's own website, this application can take several long months in order to be thoroughly reviewed ("U.S. Food and Drug Administration," 2015).

Once the IND application has been submitted and approved by the FDA, Phase 1 human trials can begin. Phase 1 human trials are an attempt to study the effects of the proposed drug on a healthy individual. These tests are utilized to determine the possible unforeseen side effects of a newly proposed drug. Participants are volunteers for the research and are typically compensated extremely well for their participation in the study. This compensation can range from a few hundred dollars to thousands of dollars depending on how severe the side effects can be, costing pharmaceutical companies millions of dollars in a short time frame. Typically, Phase 1 human trials are performed on volunteer groups ranging from 20- 80 healthy average Americans. The tests can take anywhere from a few months to 1 year in order to test the safety of the drug. If the drug is deemed safe, further tests can then continue on ("U.S. Food and Drug Administration," 2015).

Once Phase 1 human trials have concluded, Phase 2 human trials can begin. Unlike Phase 1, Phase 2 human trials do not use healthy participants; they begin using participants who express the disease or condition in which the proposed drug is intended to treat. These tests are characterized by their constant use of placebo drugs in order to determine whether or not the proposed drug is effective at all. Group participation can range from a few dozen individuals to upwards of 300 participants. Although not usually compensated, participants usually do not have to pay for the procedures at all with the hope of receiving lifesaving treatment as their compensation. Phase 2 trials can take anywhere from a few months to a few years depending on the size of the participation groups and how rare the disease that participants express is ("U.S. Food and Drug Administration," 2015).

With the conclusion of Phase 2, Phase 3 human trials begin. Phase 3 is a continuation of Phase 2 on a much larger scale. Phase 3 is a final attempt at demonstrating the effectiveness of a proposed new drug. Once again participants are not usually monetarily compensated; however, they do typically receive treatment for free. Participant groups are much larger ranging from a few hundred to upwards of 3000 people which leads to this phase being one of the most expensive. Testing of the proposed drug continues to study the side effects from Phase 1 human trials as well as attempting to study the long term effects of the drug in addition to its effectiveness. Phase 3 can last anywhere from a few months to several years depending on the amount of participants necessitated by the study. With the conclusion of Phase 3 human trials, the IND application goes through a round of post market studies ("U.S. Food and Drug Administration," 2015).

Post-market studies are performed to evaluate all of the data generated by the previous clinical trials. The studies evaluate the potential drug's safety and possible side effects, its optimal use, how it's supposed to be taken, what condition does it attempt to treat, its efficiency and how effective its intended results are on patients expressing the targeted condition. Typically, if a pharmaceutical company feels that the proposed new drug does not meet its expectations, whether they are financial in nature or medically related, this is the time where the IND application will be withdrawn. If however the company decides to proceed with the application, all of information from animal testing, clinical testing, production information and post market studies are compiled into what is known as a New Drug Application (NDA). The NDA is the official application to the FDA for the approval of the new drug to be marketed and sold within the United States. This process can be short, depending on how aggressive a pharmaceutical company decides to be with an application. Once the application is submitted, the FDA has 2 months to determine whether or not they will review the NDA. As stated by the Food and Drug Administration's own website, the FDA strives to have reviewed 90% of applications 10 months after being received. This means that for 90% of applications it takes up to an entire year to be reviewed and for some even longer ("U.S. Food and Drug Administration," 2015).

The injurious effects of the process of approving drugs by the FDA is well-documented. Often times these drugs are approved in several other industrialized nations long before they ever see use in the United States. This issue demands as much attention as the exuberant prices of the drugs themselves. One such classic example is the case of the drug called Pirfenidone. Pirfenidone is used to treat a pulmonary disorder known as idiopathic pulmonary fibrosis (IPF). IPF causes the lungs to become scarred, preventing them from functioning properly and making it difficult to breathe. The life expectancy of an individual after diagnosis of IPF is a median of 3 to 5 years (Christenson, 2012). Pirfenidone has been demonstrated as improving the symptoms of individuals with IPF and improving their respiration. Pirfenidone was not approved for use in the United States until October 2014. In comparison, pirfenidone had been utilized in other countries several years prior: Europe (2011), Japan (2008) and Canada (2012). Pirfenidone was approved in the EU based on 2 double-blind, randomized, placebo-controlled clinical trials as well as supported by 2 other Japanese clinical trials (Noble, 2011). In spite of the substantial evidence already supporting the drug and recommendations by an FDA advisory committee comprised of industry experts in 2010, the FDA decided not to approve the drug and mandated that another major clinical study take place. The results of that study were published in May 2014 and finally garnished FDA approval in October of the same year.

In addition to the redundancy experienced when approving a new drug for the first time, the unfortunate reality is that pharmaceutical companies must repeat this application process if they wish for a drug to be classified as able to treat multiple conditions. This means that every time a drug is classified as being able to treat multiple conditions, it must repeat the process of applying to the FDA as an IND application and repeat clinical trials in order to gain approval.

Take for instance Herceptin; it gained approval from the FDA in 2006 to treat HER2 positive breast cancer. At this point in time, it had just finished clinical trials, spending millions of dollars along the way, when it was determined that Herceptin could treat other HER2 positive expressing cancers, not just breast cancer. In order to gain approval from the FDA, Herceptin had to repeat clinical phases 2 and 3 for each cancer it hoped to prove that it could treat. Additional post clinical studies had to be performed as well as another NDA submitted to the FDA. This process took 4 whole years to complete and millions of dollars spent in order to prove that Herceptin was adequate at treating other types of HER2 positive expressing cancers.

The process of receiving approval from the FDA for the marketing and distribution of a new drug is cumbersome and overtly complex. The drug approval process is undoubtedly extensive, necessitating years of research and millions of dollars to be spent. A pharmaceutical company pays on average $100 million per drug in order to conduct clinical trials in an attempt to gain approval by the FDA (Herper, 2012). The amount of money spent on clinical studies increases astronomically with larger mandated participation groups. Typically, larger participation groups are necessary when a pharmaceutical company wants to prove that a proposed drug can improve upon a current existing drug marketed within the US. When the proposed drug is so close in effectiveness to a current drug, a pharmaceutical company can take advantage of statistical reporting by increasing the number of participants in order to garner a meaningful significance just barely over the existing drug. Although this strategy can allow pharmaceutical companies to market drugs against competing companies' products, these politics can tack on more to the millions of dollars spent on research, thus passing that cost onto the consumer.

The FDA was established in order to guarantee safe products for use by Americans; it currently performs in this capacity extremely well. However, the process in which it approves drugs for use is expensive, time consuming, and redundant. Balancing safety of a drug with the lives impacted including death during the review period, such as in Herceptin's case, needs to considered. At a time in history when scientific advancement has grown exponentially and new methods of study are created every day, the FDA has chosen not to change procedure and streamline its process. Medications are now able to treat on a genetic level and treatment plans are formulated and tailored to a consumer's specific DNA. Methods do exist[9] in which drugs can be well researched on faster time schedules, without the need for both phase 2 and phase 3 human trials. Just the elimination of 1 phase from the application process can save pharmaceutical companies millions of dollars and allow drugs to be brought to market sooner, saving more lives. Even miniscule gains made in streamlining the application process can correspond to huge savings for pharmaceutical companies, potentially passing on those savings to the consumer and positively impacting health outcomes sooner.

Legal Manipulations

In the United States' legal system loopholes have always been a cause for intense political debate. They allow individuals and corporations to exploit the law's shortcomings in order to circumvent various regulations to maximize corporate profit. In the pharmaceutical market, legal loopholes have sparked much heated debate due to the ethics behind exploiting them as well as the potential for huge profits that corporations can enjoy because of them. The counter-argument has always been that these loopholes in current regulations allow for corporations to protect their intellectual property as well as ensure that they are able to invest in future innovations. Countering this argument is the prolonged market exclusivity that legal loopholes allow corporations to take advantage of. By employing various strategies, a pharmaceutical company can guarantee the maintenance of its high profits at the cost of the consumer.

As explained earlier, statistical manipulation can be a useful strategy to compete against other patented marketed drugs. More often than not however, it is utilized as a strategy to maintain patents on a company's own marketed drugs. This strategy is deployed as a way of maintaining the market share on a product as well as increasing the duration of its returns. The majority of patents last a standard of 20 years, allowing pharmaceutical products to be sold unopposed until the expiration of the patent. After expiration, generic versions of a pharmaceutical product tend to appear on the market, usually undercutting the name brand's price by 40% on average, drastically reducing the returns on the name brand medication (European Commission). In recent years, several blockbuster drugs'[10] patents have been slated to expire. Despite this, several companies have filed for additional patents on those drugs, allowing them to maintain their market exclusivity in addition to keeping consumer prices high.

One such strategy of extending a patent is through the use of new formulations of a current drug. As a patent expiration date approaches, pharmaceutical companies will file for additional patents on the known compounds through different dosing that is "statistically improved" upon the older patent. A common example is the sustained-release formulations of existing drugs. For instance, when the Eli Lilly corporation faced the expiration of its patent for the antidepressant drug Prozac, the company obtained a patent and FDA approval for a once-weekly, sustained-release, "statistically improved" formulation of the drug, thus extending its market exclusivity (Gupta, 2010). Although this strategy can add some expense to a corporation due to the "research" and FDA approval needed to create the new formulation, the maintained profits of the drug greatly surpass the added one-time expense. Even at the estimated $100 million for costs in FDA approval for a weekly tablet, Prozac was still making $1.9 billion annually at its height in 2001 (Eli Lilly Corp, 2001).

Most drugs presently on the market are chiral[11] drugs comprising of enantiomer[12] molecules, meaning that of the two molecules in the chemical compound, one is the active form while the other is typically ineffective. Drugs that comprise of equal parts of enantiomers are considered racemic drugs. Racemic drugs are composed of dextrorotatory and levorotatory forms of a compound in equal proportions. Companies that have racemic drug patents that are about to expire often choose to market

the single effective enantiomer under a different patent. This process is called a chiral switch. One prominent example of a chiral switch is AstraZeneca's racemic drug, omeprazole (Prilosec), which was originally approved in 1989. Prilosec was earning over $6 billion annually in 2000 by the time its market exclusivity was about to expire in 2001 (Berenson, 2005). In 2001, Astra Zeneca was granted FDA approval to market esomeprazole (Nexium) comprising of the single active enantiomer from Prilosec. The strategy proved successful as it allowed Astra Zeneca to gross a mean of $6.8 billion[13] between the two drugs during the years 2003-2011. This is showcased in Figure 12:

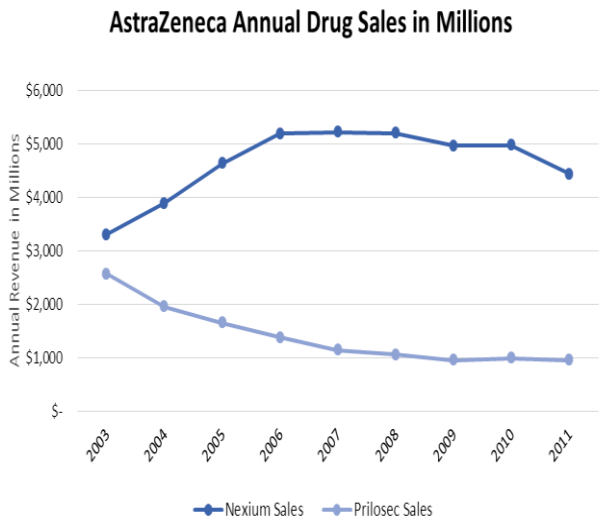

Figure 12: Totals were taken from public released filing statements from AstraZeneca and represent total gross revenue from each pharmaceutical product.

Most shocking is the fact that Nexium has been cited as having no clinical benefit over its predecessor Prilosec (Goozner, 2004). This showcases a prime example of a loophole in our current legal system that allows for the gross misuse of funds in order to maintain profits on extremely dated innovations rather than the creation of newer and more clinically beneficial treatments.

The added cost to consumers due to elongated market exclusivity from loopholes in the U.S. legal system is significant. As showcased, corporations are able to maintain high profits compared to relatively low cost, meaning that employing strategies like these will continue throughout the entire industry, stagnating competition within the market. Without generic drug competition in the market, the prices of name brand medication are allowed to stay high, maximizing corporate profits. The ethics debate aside, the relative ease of attainment of these legal loopholes with minimal planning ensures that this flaw in the system will be utilized by the industry until it is corrected. The ability for a pharmaceutical corporation to maintain market exclusivity on its product also resonates with the lack of price control regulation within the US.

A World View of Healthcare Cost Containment

In addition to loopholes, price control regulation of pharmaceutical products has been a topic of heated debate in U.S. healthcare policy for several years. Price control regulation pertains to any control that a government extends over the price of a product. Proponents for price control regulation on pharmaceutical products make the argument that regulation will help to reign in the exuberant prices experienced by consumers. Critics, on the other hand, make the claim that price controlling will stifle future innovation, harming future generations. In essence, the debate has become the short-term gain of the current generation versus the long-term gain of future generations. The fact of the matter is that several industrialized nations who are competitive with the United States in terms of health care, utilize price control regulation in order to reign the costs of pharmaceutical products.

It is clear that pharmaceutical corporations do play a key role in funding and conducting clinical trials that are needed to develop a new pharmaceutical product. However, it is important to note that the fraction of pharmaceutical revenue that is allocated to research and development typically falls below 20 percent. The share of funding that is spent on basic research that creates innovative new compounds is significantly less (Light, 2005). According to a research article analyzing 26 drugs approved by the FDA between 1984 and 2009, the majority of drugs had received some form of federal government funding. Many of the discoveries had been made by academic researchers who were supported by grants from federal entities like the National Institutes of Health (NIH), while others yet were jointly funded by the federal government and commercial institutions, with the fewest proportion being solely funded by the pharmaceutical industry (Kesselheim, 2015). Furthermore, there is little evidence showcasing an association between research and development costs and the exuberant costs of the drugs (Keyhani, 2006). This showcases that pharmaceutical products are priced in the United States off the basis of what the market can bear.

Germany serves as a prime model for price regulation due to the similarity of its health care model[14] to the United States' private insurance reimbursement model. The first iteration of a form of price control regulation in Germany occurred in 1989 with the Gesundheitsreformgesetz[14] (GRG); the GRG saw the implementation of Festbeträge or "reimbursement amounts." The GRG functions by setting a maximum reimbursement amount that sickness funds will pay for pharmaceutical products. This is accomplished by grouping together "clusters" of pharmaceutical products at three levels of criteria:

1. Products with identical active ingredients and similar administration modes.
2. Products with similar therapeutic or pharmacologic active ingredients.

3. Products with similar therapeutic effects.

Once a maximum reimbursement is set for a Festbeträge cluster, pharmaceutical corporations are allowed to set whatever price they choose. If the corporation sets a price above the Festbeträge, it is up to the German consumer to pay the difference in cost. In addition, it is mandated that a physician must inform the consumer if a product in a cluster is above the Festbeträge before prescribing the medication (Paris, 2008).

This model exemplifies the German's pursuit of efficiency. By grouping together products of similar therapeutic benefits into clusters, it ensures that patients are able to receive the medication they need at affordable prices stemming from competition created between cluster drugs. The utilization of reference price groups is so effective that in 2005, only 1,975 pharmaceutical products of 27,908 included in the maximum price scheme, had prices that were over the Festbeträge (Paris, 2008). This means that only 4% of products offered require additional payment by the consumer.

The use of Festbeträge clusters may also have the added benefit of dissuading the creation of redundant medications (especially products created for the sole use of maintaining market exclusivity) that possess similar therapeutic benefits.

Due to the risk of not being reimbursed for their product, pharmaceutical corporations are dissuaded from developing additional drugs in a particular cluster that show no improved therapeutic benefits over competitive drugs.

Germany is not the only country to make use of various price regulation strategies. In fact, most industrialized countries utilize a price regulation scheme. From the United Kingdom to France to Japan to our northern neighbor Canada. The United States is one of the only countries to not utilize a price regulation scheme when it comes to pharmaceutical products. The truth is that this reality is taken advantage of constantly by pharmaceutical corporations, routinely punishing the American consumer.

Without explicit price control regulation, pharmaceutical companies have been allowed to inflate prices without substantial reason at all. There have been several examples of this phenomenon in the past decade. A recent case is the case of Martin Shkreli and Turing Pharmaceuticals. Traditionally used to treat Toxoplasmosis[15], which is typically found in individuals with HIV/AIDS or some cancer patients, Pyrimethamine has been available in the United States since 1953. In 2015, Turing Pharmaceuticals acquired the rights to the 62 year old drug from Impax Laboratories for $55 million (Pollack, 2015). Almost immediately on acquisition, Turing Pharmaceuticals imposed a price increase from $13.50 a tablet to $750, an almost 5,500% increase (Pollack, 2015). Although this is an extreme scenario, this is not the only case of unexplained price increases.

Another example of price gouging by a pharmaceutical company would be the steady increase of the pharmaceutical product, Epipen. Originally approved in 1987 by the FDA, Epipen has been synonymous with epinephrine autoinjectors everywhere (FDA Approved Drug Products, n.d.). Acquired by the Mylan corporation in 2007, the price of the 30 year old autoinjector has skyrocketed from $108.93 in 2008 to $679.71 in 2016, according to data reported by Medicaid Services (Drug Utilization 2008-2016 – National Totals, n.d.). This is showcased in figure 13:

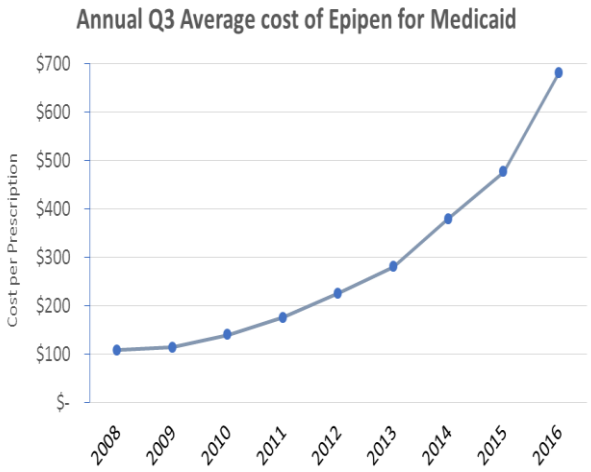

Figure 13: Data obtained from Fee-for-Service Utilization (FFSU) annual Medicaid spending in Q3 on EPIPEN 2-P.

This 500% increase in price has left patients reeling as they struggle to afford the lifesaving drug. Due to rigorous marketing and price hikes, Mylan was able to take a pharmaceutical product barely grossing $200 million in 2009 to grossing comfortably over $1 billion in 2015 (Lipton, 2016). Although epinephrine itself has been utilize as a pharmaceutical product since the early 1900's, Epipen has dominated the market as there is currently no equivalent competitor (Lipton, 2016; Sneader, 2001).

Although one would hope that Mylan and Turing Pharmaceuticals are just two outliers when it comes to drastic price increases on their products, the unfortunate reality is that there are several more documented case examples of similar practices by other pharmaceutical companies. Drug manufacturers are able to take advantage of Americans with little to no consequence dictated by the Federal government regulation. Price control regulations, like Germany's, could be an effective tool in assisting the US in reigning in exuberant costs of pharmaceutical products.

CONCLUSION

The gross difference in pharmaceutical expenditures between the United States and the rest of the world can be attributed to one main attribute: ineffective regulation. The inefficiency in regulating entities and the lack of regulation all together are the main reasons that American consumers are forced to account for greater proportions of the revenue of the pharmaceutical industry. The pharmaceutical corporations cannot inherently be blamed themselves due to the fact that they are for-profit entities. In the end, a business' decision-making objective is to maximize profits and increase shareholder value. All businesses, including the pharmaceutical industry, will use every legal means to meet these objectives, including taking advantage of loopholes within the current U.S. system.

The "silver bullet" in healthcare reform is not in socialized medicine, price mandates, advertisement restrictions, or any one approach. While regulation is the main reason for high prices, an effective solution cannot solely target regulatory practices. The solution to the high cost of U.S. pharmaceuticals takes a multi-pronged approach that will include:

1. Patent Reform: Materially similar compounds and/or therapeutic outcomes will not be allowed monopoly rights after the initial patent period.
2. Regulation Reform: The European model for reimbursement and cost control should be implemented for all government-paid prescriptions and this should be the standard rate for private insurance payments.
3. Direct-to-Consumer (DTC) Advertisement: Direct drug advertisement has done more consumer harm than any beneficial education aspects. A 30 second commercial is not the format to properly educate a consumer about a drugs' potential benefits and risk for an individual consumer.
4. Drug Approval Reform: Current drug development methods are unduly arduous, complex, and lengthy which directly inflates the cost for development. Streamlined methods of testing new compounds should be considered along with computer modeling approaches that can modernize and accelerate testing outcomes while greatly reducing costs.
5. Consumer involvement: without consumers having a financial incentive in the cost containment process, the overall impact of drug cost reform will be muted at best. Consumers, including government-aid consumers, must take an active role in healthcare cost reform. Combining education including pricing guides, cost benefits, rebates, and other incentives, consumers can be influenced to seek generic drugs over brand name, implement lifestyle changes to eliminate the need for certain drugs, and employ prevention efforts to avoid escalating drug prescriptions. Hospitals and Doctors must serve as patient advocates and work together to minimize costs while meeting the patient needs with a plan to determine the lowest cost maintenance plan, reduction in dosage, or non-reliance on the drug with improved health.

Ultimately, the scenario that Americans currently find themselves in is due to complacency and a lack of education about the current position of the pharmaceutical industry as a whole. When the industry is not continuously challenged and refined with effective regulation and/or market controls to meet changing societal needs, costs grow rampant. When this occurs, the industry becomes unresponsive to its consumers and only responsive to profit maximization. This is precarious due to the nature that there will always be a demand for health care products. If the current scenario is allowed to continue, prices will be allowed to increase, further punishing the American consumer and exacerbating the healthcare crisis.

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