Faith & Reason Honors Program

SENIOR THESIS

Name
Brenda Haggerty

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Thesis Director
Rodger Berg, Ph.D. (Chemistry)

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Introduction

I’m a member of the second generation to spend their entire life “living better through chemistry.” Every month a commercial for some new oddly-named medicine pops up on TV promising to cure what ails you, and are quickly followed by commercials promising a way to help you afford those drugs. I grew up in a world where the pharmaceutical companies were the bad guys, wringing the elderly for their pensions and conning doctors into prescribing their medicine more often. So when, after three years of being a chemistry major in the time of Big Pharma, I found myself defending the drug companies’ high prices and attempts to block generics from getting on the market to a relative, I decided to take a closer look at how drugs became such a ubiquitous part of our daily lives.

The one aspect that really separates the past hundred or hundred fifty years from prior history is the perception of medicine. For much of history, healing was an art. It depended on a combination of mysticism, religion, and knowledge of herbal remedies passed down from generation to generation. The beginning of Western medicine did not stray too far from its precursor, depending on tonics and elixirs whose effects on patients were as often deadly as they were curative. A greater understanding of chemistry and how the body works led to the development of new, more effective, safer medicines. As the new medicine rose to prominence, the old holistic methods started to take a back seat.

At the same time chemistry was promoting the development of medicines, it was also changing the way we eat. Preservatives not only kept food from spoiling,
they could make bad food look good, or unripe produce look ripe. Canning, cooking, and freezing changed the way Americans ate. Flavors, sweeteners, and dyes became commonplace in the supermarket. As the steps between the farm and the table grew, familiarity with how food affects us shrank. An increase in the availability of processed food, coupled with a decrease in daily activity and fresh foods, contributed to a number of health problems such as heart disease and diabetes.

Pharmaceutical companies were willing to exploit the newest medicinal discoveries for their drugs. As the diseases and disorders that had plagued the population were treated – sometimes to the point of becoming obsolete – the population began to live longer. The drug developers turned to treating the “new” diseases that became the focus of a country that was living longer yet less healthy lives, looking not just at our physical health, but our mental health as well. While people throughout history looked for ways to make life better, easier, prettier, or skinnier, modern drugs held the promise of chemistry behind their claims, and search for magic bullets still continues.

As new drugs are developed and old ones fall to the wayside, a greater understanding of drug interactions and unwanted side effects is dawning. The question of whether to keep substances legal and available to the public has been a contentious one for centuries. When it comes to drugs that not only alter our physical state but our mental state, science becomes less important than politics, religion, racism, and fear. In America, drugs straddle a tenuous line between the Food and Drug Administration and the Drug Enforcement Administration. The
FDA regulates the safety, efficacy, and labeling of food, drugs, and cosmetics; it is the “science” end of government regulation. The DEA is the “law enforcement” end; it says what is legal and illegal and enforces the regulations. The two are not exclusive. Drugs approved for medicinal use appear on all but the first of the DEA’s schedules for restrictions, and various drugs such as tobacco are not under the FDA’s control at all, as of the moment.

The Beginning of the FDA: Using Fear to Make a Change

Although states had attempted to regulate the food being sold to their residents since the 18th century (starting with Massachusetts in 1785), the United States federal government did not have any legislation dealing with the distribution of food or drugs until 1906.¹ A number of illnesses traced to bad food in the preceding decades had brought the call for oversight but political and industry pressure continued to table the bills.

Starting in 1867, under the umbrella of the Department of Agriculture, the Division of Chemistry was charged with monitoring suspected tampering of agricultural products. The Division started to come into its own with the appointment of Harvey Wiley in 1883, a vehement opponent to the use of adulterants in food. Those included most of the preservatives used in food at the time. Wiley demonstrated the questionable safety of food adulterants with his ten-part *Food and Food Adulterants*. In this study, he used the ethically dubious
method of feeding healthy volunteers various amounts of preservatives to gauge their health effects.²

1906 saw the publication of Upton Sinclair’s *The Jungle*, a novel intended to inspire Americans to take to Socialism. While the last half of the novel tells of the protagonist’s redemption through a Socialist society, most readers were struck by the first half of the book. The graphic scenes of the meat-packing plants, with rats – and rat poison – falling into the meat processors, and inspectors ignoring spoiled carcasses passing through the plant, were enough to push both public and political sentiment towards regulation.

The Food and Drugs Act passed that year focused less on the actual quality of the food being produced for mass market and more on the labels on that food. Any substance designed to trick the consumer by hiding damage or rot, or deemed unsafe, became illegal, and any formulation containing any of 11 drugs including cocaine, alcohol, marijuana, and opium had to be labeled with the content.³

Wiley was much more concerned with contaminants in food than in drugs, which was understandable considering the toxicity of some of the additives being used to preserve food or make it look better. After he left the office in 1912, attention turned more towards the snake oils being sold as miracle cures with little oversight as to ingredients or efficacy.⁴ While the 1906 act required accurate labeling in regards to what the drug formulas contained, the act gave government no power to monitor a drug’s therapeutic claims. With little or no testing to prove if
a drug worked or was safe, the expanding market for cures and cosmetics was a disaster waiting to happen.

And indeed, disasters did happen, again and again. In an effort to create a law which would give them the powers to protect the public, the FDA of FDR’s administration created the “American Chamber of Horrors” in the mid-1930’s. This exhibit, open to the public, exposed the deceptive practices the food industry used to make its products more appealing. Canning food allowed substandard produce and meat to be sold alongside higher quality foods without the consumer being able to compare quality. Preservatives made meat look fresh beyond its natural shelf life, and clear packages were lined with prime cuts while less choice pieces were hidden underneath. Alongside the foods were the stories of cure-all drugs that caused death, such as Radithor, an elixir which contained radium and caused the radiation poisoning death of a wealthy New Yorker who took it regularly. Graphic displays showed the results of unregulated cosmetics, such as Lash-Lure, a dye designed to darken the eyelashes, which resulted in women losing their sight.

Some viewed the exhibit of the extremely liberal Roosevelt government as propaganda for support of a stronger regulatory act, and rightly so. It primarily existed to rile the public and spur the government to action. However, the “horrors” the exhibit showcased were taking place and even considering the viewpoint of food and drug manufacturers – and their votes – it was obvious something needed to be done about fraudulent claims and misleading, if technically accurate, labeling.
The final push came in the form of a sulfa medicine designed to appeal to children. Although sulfanilamide was a tried and true medicine for treating streptococcal infections in its solid form, demand rose for a liquid form of the medicine. In 1937, a Tennessee pharmaceutical company, S.E. Massengill Co., found a solvent into which the sulfanilamide would easily dissolve. The resulting liquid looked and smelled nice and best of all, tasted like raspberries. Elixir Sulfanilamide was immediately sold that September to doctors around the nation.⁹

Within a month, reports of deaths associated with Elixir Sulfanilamide began rolling in. The American Medical Association investigated the reports and requested the formula from S.E. Massengill Co. The solvent that tasted so nice was diethylene glycol, one of the primary components of antifreeze, and it was now being sold as the newest sulfa medicine.

Elixir Sulfanilamide was pulled off the market in October. In the two months it had been sold and prescribed to patients, over 100 people died. Of the 240 gallons manufactured, almost all but the amount consumed was retrieved. The formulation had been sold with no testing of its effects, either medicinal or poisonous. Even background research into the solvent could have revealed recent studies showing diethylene glycol’s toxic properties. Yet, the only action the government could take against S.E. Massengill was incorrectly labeling the medicine an elixir despite not containing any alcohol. If the product had been named correctly, there would have been no recourse for the victims.
Dr. Massengill, the owner of the company, coldly denied any wrongdoing, leaning on the fact that they had not technically violated any laws. A letter from one of the prescribing doctors gives a sense of how the rest of the country reacted:

“Any doctor who has practiced more than a quarter of a century has seen his share of death. But to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have known hours when death for me would be a welcome relief from this agony.”

(Dr. A.S. Calhoun, October 22, 1937)

The scientist who developed the elixir shared Dr. Calhoun’s despair and in the aftermath of the deaths committed suicide.10

The Elixir Sulfanilamide tragedy displayed the gaping holes in the 1906 legislation and was the catalyst for the 1938 Food, Drug, and Cosmetic Act. This new Act required new drugs to be tested for efficacy and safety before being marketed, as well as enforcing truth in labeling in regards to curative properties. Food standards became enforceable and allowable levels of dangerous substances were addressed. Cosmetics and medical devices were now also under the eye of the FDA and required to be tested for safety.11

The most prominent and successful effect of the new laws became evident with the drug thalidomide. This anti-morning sickness drug was sold throughout Europe and Canada, which at the time did not have agencies like the FDA in place.
In the United States, the FDA did not approve thalidomide. The reviewing officer was not convinced that the drug was safe. Reports emerged from Europe of the birth defects now synonymous with the drug’s name and the drug never received approval. Thanks to the FDA’s vigilance, only 17 babies were born with thalidomide effects in the United States. The drug had been imported from other countries.\textsuperscript{12}

With the rise of an FDA with enforcement behind it came the distinction between over-the-counter and prescription drugs. It also made the job of the FDA much harder than before. Enforcement of food and drug regulations required field work, as well as battling the sales of outlawed drugs. The new drug applications flooded into the department. A number of amendments gave the FDA increasing control over the distribution of drugs and the trials used for the approvals.\textsuperscript{13}

The presence of new chemicals added to food and new therapeutic drugs expanded along with the FDA’s roles, and eventually the department became unwieldy. Throughout the 1960’s and 70’s, new agencies like the Consumer Product Safety Commission were formed to ease some of the FDA’s burden. In 1973, President Richard Nixon created the Drug Enforcement Administration with an Executive Order and took the duty of enforcing the regulation of illegal drugs from the FDA.\textsuperscript{14}

The formation of the DEA was not necessarily the opening volley of the war on drugs – not in the country which had seen women teetotalers destroying bars with axes – but signaled the entry of heavy artillery. Unlike the FDA, which sought to protect citizens’ health from both ignorance and deliberate misleading through
scientific testing, the DEA was strictly law enforcement. Drugs were fit into schedules, depending on their medicinal use, the potential for abuse, and potential for physiological or psychological dependence. These schedules determine penalties for possession and distribution, and also determine which drugs must be supplied by prescription and which can be made available over the counter. Many commonly available drugs, such as aspirin, ibuprofen, nicotine, and alcohol are not scheduled; this does not necessarily mean they would not fit into one of the schedules.

The current arraignment of government agencies spreads the responsibility for oversight among many agencies. The FDA regulates food labeling and safety, drug manufacturing, approval, and labeling, cosmetics, medical devices, veterinary supplies, and the nation’s blood supply. The Department of Agriculture takes care of meat and poultry, the CPSC covers consumer goods, the ATF monitors alcohol and tobacco, and the DEA enforces laws regarding drugs of abuse.

The FDA and the DEA have some overlap when it comes to drug scheduling. While the schedules are used mainly to determine the seriousness of a drug offense, it is clinical trials run under the FDA’s drug testing standards that can determine medicinal use and potential for addiction. A drug that is not manufactured, after all, will remain a proprietary formula on a disk and not a pill in a pharmacy. Also, prescription drugs straddle a fine line where their legitimacy can change depending on a doctor’s signature.
Monetary Manipulation: Research Funding

The FDA is a government agency and a political entity. Its very creation and development is steeped in political manipulation. The FDA relies on federal funds granted by politicians that more and more are being influenced by lobbyists. Among the “Big” industries – Big Tobacco, Big Oil, and so on – Big Pharma has emerged in the past few decades as one of the biggest.

A pharmaceutical company is particularly dependant on the government for its profits. Billions of dollars are spent developing new drugs to address untreated condition or to improve current treatments. Only a fraction of the compounds developed in a drug company’s research and development labs will make it to in vivo testing, and of those, only a few make it to human clinical trials. This development process, even before being able to apply for FDA approval, can take ten years (in fact, Merck’s seven-year development and approval of the Type II diabetes drug Januvia was hailed for its speed). The drug company makes an enormous investment of time and money banking on their approval for sale in the USA. For a smaller pharmaceutical company, a rejection of a new drug can put them out of business. Larger companies can absorb the financial hit but as in any business, a loss of potential earnings and brand exposure can have lasting effects.

A 1996 study addressing drug approval times found that “experienced” companies – those applying for about one new drug approval a year – had shorter approval processes than naïve companies. Part of this can be attributed to
experience with the application process, making sure the paperwork is correct and such. Part of this, though, depends on the companies’ influence. The FDA will approve a drug without all the required studies on the promise that the necessary studies will be carried out. 87% of these studies are never conducted.17

Why doesn’t the FDA enforce the required trials? The FDA is an administration under Congress’s oversight. The FDA’s power is limited by Congress and Congress is influenced by lobbyists, including the big pharmaceutical companies. One FDA officer told the watchdog agency Public Citizen of the futility of enforcement:

“My office director told me that he was going to overrule me because the sponsor [a drug company] would just go over our heads to Capitol Hill. He felt it was best to approve the drug for an indication not studied and have the sponsors do a Phase 4 post-marketing trial in support of the indication. I reminded him that this sponsor had failed to honor other Phase 4 studies. He went ahead and approved the drug.”18

It is often not until research studies are conducted to seek approval for further uses that problems may be found with a drug.

Further compounding the problem, the research given to FDA is provided by the company seeking approval. These studies are funded by the companies and often, funding is attached to favorable results. As we entered the twenty-first century, 70 percent of medical research was funded by the drug companies.19 There is a legitimate concern that academic research has become a commodity to be bought and sold.
Government Manipulation: Aspartame

Like most large organizations, the majority of people working at the FDA do their job with the intent to do the job the FDA was created to do. Mistakes do occur but they are unintentional and if caught, fixed. It is the people at the top, the ones whose jobs depend on staying in the good graces of the government and the lobbyists, who have the tendency to deliberately manipulate the system. When the pressure to please the people who gave you your job increases, good science – and good intentions – can go out the door. Questionable product approvals are not always as noticeable as the Vioxx scandal, however, but closer looks can reveal troubling events, even in the seemingly most innocuous of places.

In 1965, a scientist working at G. D. Searle and Co. was developing an anti-ulcer drug. One of the compounds got on his fingers, and upon tasting it, he realized it was very sweet. The pressure to put an artificial sweetener on the market to replace the cancer-causing cyclamate pushed the compound through development and in 1974 aspartame was approved for addition to powdered foods.20

Further study on the sweetener showed that during metabolism, the structure breaks down into aspartic acid, phenylalanine, methanol, formaldehyde, and formic acid.21 Studies on animals as well as anecdotal evidence suggested that consumption of aspartame could have an effect on brain tumors. The studies that showed this had been suppressed before its approval, but with the increased exposure of the public to aspartame, the worries resurfaced.
The FDA reviewed the evidence before them. They determined that, given the number of reports of health problems and the lack of sufficient safety studies, to take away aspartame’s approval in 1980. Given the widespread use of artificial sweeteners, the loss of aspartame was a big hit to Searle’s profits.

Meanwhile, G. D. Searle CEO and former White House Chief of Staff Donald Rumsfeld had been named as a part of Ronald Regan’s transition team. The day after Regan took office in 1981, Searle reapplied for approval for aspartame. Less than a week later, the FDA commissioner from Carter’s administration was replaced with Dr. Arthur Hayes, who was formerly contracted with the Department of Defense. Within his first six months aspartame was once again approved and in 1983, the use of aspartame in soft drinks was approved.

The timeline may look coincidental; after all, aspartame was just taken off the market the year of Regan’s election. However, testimony from a former Searle saleswoman casts a different light on the matter. Patty Wood-Allott said of Rumsfeld “If necessary he would call in all his markers and that no matter what, he would see to it that aspartame would be approved that year.”22 The approval went ahead despite plenty of protests.

Aspartame was and still is a matter of controversy. Among other things, one metabolite, phenylalanine, is harmful to people with phenylketonuria. This is the reason for the warning on diet drinks stating that the drink contains phenylalanine. There is still the open question of whether aspartame causes brain tumors. Studies submitted to FDA on the subject had a number of deficiencies, including missing rat
fetuses and lost data. (Perhaps the most amusing and yet troubling datum in the FDA’s Bressler Report is the life span of one animal subject: “Observation records indicated that animal A23LM was alive at week 88, dead from week 92 through week 104, alive at week 108, and dead at week 112.”

Other studies concern the degradation of aspartame into methanol. Correlations between levels of diet soda consumed by soldiers in the Gulf War and a rise in health problems have been suggested as a cause of Gulf War illness. Other studies have shown evidence that ingestion of aspartame could increase susceptibility to or intensity of seizures. What could be most telling, however, is that while 92% of independent studies showed some kind of problem related to aspartame, none of the industry-sponsored studies – the ones submitted to the FDA – showed problems with aspartame.

The big questions about aspartame – it is safe? At what levels? What adverse effects may it have? – may not be answered any time soon. While there is blatant political interference in the aspartame approval process, it could be dismissed as a one-time thing. When one looks at G. D. Searle & Co.’s history, however, a troubling trend emerges. Among Searle’s products are the first birth control pill and Celebrex (while partnered with Pfizer), both known for problems encountered after being put on the market. Birth control pills were originally marketed at dosages far higher than necessary for most patients and high dosages have been related to various forms of cancer in women. Celebrex and its related drug Vioxx will be discussed in detail later.
More recently, Searle became a wholly-owned subsidiary of the Monsanto Company. Monsanto has received criticism for pushing genetically engineered crops such as Roundup Ready corn (Monsanto also manufactures Roundup) before testing whether the introduced genes could have adverse effects on consumers. Searle has a history of presenting drugs for approval which need further study to be safe.

Dr. Philip Brodsky, the head of the FDA task force that investigated Searle’s practices, stated that he’d “never seen anything as bad as G. D. Searle’s studies,” and his colleague Dr. Alexander Schmidt stated that they “were incredibly sloppy science. What we discovered was reprehensible.”27 Searle’s approach to product development and approval was not just a matter of ignorance, or poor training. The company philosophy was taking the shortest, if most reckless, route to approval. A 1970 memo from a company executive describes their process:

“The basic philosophy of our approach to Food and Drug should be to try to get them to say ‘yes,’... even if we have to throw some [questions] in that have no significance to us other than putting them into a ‘yes’-saying habit. We must create an affirmative atmosphere in our dealing with [the FDA]. It would also help if we can get them to get the people involved to do us any sort of favor, as this would also bring them into a subconscious spirit of participation.”28

This sense of bending the FDA to the company’s will must give pause. One hopes that the government will protect the citizens of its country. But, the government is after all made of humans and when a company is out to deliberately mislead the FDA, it is even more susceptible to manipulation. Add an
administration willing to “help old friends” and the recipe for dangerous product approvals is in the works.

Scientific Manipulation: Vioxx and the COX-2 Inhibitors

As the American population ages, more and more people are forcing problems such as heart disease, arthritis, and Alzheimer’s disease. While many medicines have become necessary to keep a patient alive, there are a fair amount of drugs that fall under quality-of-life issues.

Arthritis is a common problem with age as joints are exposed to decades of wear. Most cases of arthritis are treated with general pain-killing drugs called non-steroidal anti-inflammatory drugs (NSAIDS) available over the counter such as naproxen or ibuprofen. However, these common NSAIDs can lead to the erosion of the inner lining of the stomach, causing ulcers. Drug companies looking to fill the demand for stronger, safer drugs developed drugs like Vioxx and Celebrex, marketed specifically treat the pain of arthritis, and designed to not erode the stomach lining. These drugs made it through the initial testing to human trials, all run by Merck and Pfizer, respectively.

After being proven effective in a number of clinical trials, Vioxx was approved as a prescription drug in May 1999. Earlier in the year, Merck had started a long-term study called Vioxx Gastrointestinal Outcomes Research, or VIGOR. Although preliminary results seemed to show Vioxx both safe and effective as compared to naproxen, by the end of the year the study resulted in the conclusion that patients
on Vioxx were about twice as likely as those on naproxen to experience serious heart problems. Members of the safety committee overseeing the study questioned the results, postulating that naproxen had a heart-protecting effect, thus making Vioxx look more dangerous than it was.\textsuperscript{29}

Merck published their results in both the New England Journal of Medicine and the Journal of the American Medical Association, leaving out three of the heart attacks Vioxx patients suffered and neglecting to mention other non-heart attack cardiac events. Meanwhile, independent cardiologist reevaluated the data from VIGOR and concluded that naproxen had not exhibited a heart-protecting effect. This placed the explanation for the doubled rate of heart problems back on Vioxx.\textsuperscript{30}

It wasn't until five years after the FDA approval of Vioxx that anecdotal stories of increased cardiovascular risk were supported. Vioxx was being tested for anti-colon polyp activity in a study titled APPROVe when the increased risk of heart problems could no longer be ignored. The study showed a rise in heart attack risk after 18 months on the drug. The study was stopped for the participants' safety.\textsuperscript{31}

After a meeting with FDA officials in September of 2004, Merck announced that it was voluntarily withdrawing Vioxx from the market.

The following two years saw the argument degrade into a polite shouting match between the medical journals that had published Merck's articles and the authors of the VIGOR study. The journals repeatedly called for a correction of the
data while the authors defended their study design and results. Vioxx has not been returned to the market.

About the same time as the Vioxx drama was playing out, one of Merck’s competitors was facing a similar situation. Pfizer’s Celebrex, another COX-2 inhibitor marketed for the easing of arthritis pains, had been approved by the FDA in December 1998. In 2000, Pfizer submitted another COX-2 inhibiting NSAID for FDA approval; Bextra was approved in November of 2001. In 2004, Celebrex was also undergoing clinical trials to test its efficacy in preventing colon polyp growth. Primary findings in one of the trials suggested that Celebrex may cause an increase in cardiac risk; with the Vioxx withdrawal occurring so recently the FDA decided to halt the study while allowing a second one that had not showed the similar risk to continue.

The eventual results of the clinical trial showed Celebrex did have preventative effects on the development of familial colon cancer. However, the increased risk of cardiac events and limited range of effectiveness makes the drug a poor choice for a preventative measure. The real effects of the clinical trials, though, reached beyond cancer prevention. Following on the heels of the Vioxx fiasco, clinical results suggesting an increase in heart risk brought attention to all the COX-2 NSAIDS, including both of Pfizer’s drugs.

Pfizer presented research to the FDA about Celebrex’s safety during the 2005 review of the pain killers. None of their studies showed any danger. Pfizer’s president Dr. Feczo did acknowledge that their may be outside studies showing
different results but stood by his company. Among Pfizer’s sponsored research was a
study done with Alzheimer’s patients in 1999. The study showed an increase in
heart risk. It was never published.33

Even through 2004, the FDA allowed Bextra to stay on the market. The
warnings on the label were updated to include the increased risk of cardiac event,
as well as warnings about the increased occurrence of Steven-Johnson syndrome
and toxic epidermal necrolysis, two serious skin reactions. Eventually, in April of
2005, Bextra was removed from the market.34

While Bextra was removed, Celebrex was allowed to stay on the market. The
level of the drug used in the colon polyp study, 400mg, is twice the normal amount
prescribed for arthritis sufferers. Celebrex proved to have the least adverse side
effects (Vioxx being the most dangerous) and though still available, was given a
black box warning on its label. Black box warnings are the strongest warning the
FDA can place on a label and detail the dangers of a drug’s side effects. In 2006,
even with the black box warning, the FDA approved Celebrex for use in children as
young as two years old suffering from juvenile rheumatoid arthritis, a crippling
disease, despite the risk of heart problems.35

The votes from the FDA advisory panel that evaluated the drugs in 2005 are
somewhat alarming. Ten of the 32 advisors had worked at institutions that received
money from either Merck or Pfizer. The advisors with ties to these companies voted
9-1 to keep both on the market; the rest of the panel voted 14-8 for Vioxx and 12-8
for Bextra to be removed from the market.36 When asked, the advisors denied that
their ties to the companies affected their vote. The FDA noted the difficulty of finding people qualified to assess drugs – those who have performed research on pharmaceuticals – who have no conflict of interests. Furthermore, an FDA safety officer said he received pressure from his superiors to not present his recent findings regarding the painkillers’ cardiac dangers in front of the committee.  

Merck has not quite learned its lesson from Vioxx. The company has recently put its drug Arcoxia, selling in 43 countries, up for FDA approval. An extensive study showed triple the heart problems as naproxen and no increase in pain relief. The FDA voted 20-1 to reject the drug.  

Pfizer also did not learn its lesson. In 2008, evidence in a Boston court case showed that Pfizer attempted to suppress studies showing their drug Neurontin ineffective for chronic nerve pain. The drug was an effective if not widespread epilepsy drug and in 2004 a generic version was approved. About the same time Pfizer began promoting off-label uses for the drug, including chronic pain. However, most of the studies showed little efficacy. Some studies were rejected from publication due to blatant bias, while other articles were written by company representatives rather than the scientists performing the research. The case concluded that Pfizer controlled the amount of information doctors received by suppressing or re-writing studies to appear more positive.  

At least those studies were conducted. Dr. Scott Ruben practiced at Baystate Medical Center and was an anesthesiologist known for the amount of research he conducted. From 2002 to 2007 Pfizer underwrote much of his research funding for
drugs like Celebrex and Lyrica. In March 2009, it came to light that much of the findings Dr. Ruben published contained fabricated data. A spokesman from Pfizer stated that “as part of such research, we count on independent researchers to be truthful and motivated by a desire to advance care for patients. It is very disappointing to learn about Dr. Scott Reuben’s alleged actions.” Former editor of the NEJM, Dr. Jerome Kassirer, responded to the news differently: “When researchers are beholden to companies for much of their income, there is an incredible tendency to get results that are favorable to the company.”

**Definition Manipulation: The Semantics of Addiction**

An important aspect of a person’s relationships with drugs of all types is the concepts of dependence and addiction. Not only important to consider in developing and prescribing medicines or treating users, a drug’s tendency to cause dependence or addiction is integral to the DEA’s scheduling system. However, the ideas of what dependence and addiction mean have changed through the years. Further compounding the situation is society’s approval of certain types of addictions and condemnation of others, which change from culture to culture and decade to decade.

The term addiction has fallen out of favor recently for psychologists due to its vague nature. Instead, a distinction has been made between the physiological and psychological effects something has on a person. Both physiological and psychological dependencies require regular, repeated exposure to the addictive substance. The difference lies in the results of stopping the drug.
A person who is psychologically dependent on a substance strives to attain the feeling the drug gives them. The experience of the high is enough to entice regular use and can lead to typical addiction behavior like devoting time to ensuring a supply of the drug or feeling low without the drug.\textsuperscript{41} A person who is merely psychologically dependent does not necessarily get the physical symptoms indicative of withdrawal when exposure to the drug is stopped.

Physiological addiction leaves its chemical mark on a person’s brain. Regular exposure to the drug causes changes in the body’s expression or recognition of neurotransmitters. It is not necessarily the high that keeps a person coming back to the drug but the desire to keep away the low. When a person is physiologically addicted, stopping exposure to the drug will cause physical withdrawal symptoms ranging from headaches to delirium tremens and, in some severe cases, death.\textsuperscript{42}

Drugs which the body flushes easily – alcohol, for example – and that are physiologically addictive will cause the typical withdrawal symptoms unless the patient is weaned off of the drug. This is what makes quitting cold turkey hard or even impossible for most people. It also is the reasoning behind methadone treatment for opiate addiction. Methadone acts as a substitute to stimulate the receptors without having the psychoactive effects of morphine or codeine, allowing the addict to step down the amount of methadone until the addiction is under control.

Drugs which are fat-soluble – tetrahydrocannabinol is a prime example – are stored in the body’s fat reserves and are not flushed out of the body quickly. This
can often lead to difficulties in determining whether or not a drug is physiologically addictive. Drugs stored in the body will continue to leach into the bloodstream even after the drug is no longer ingested. As the amount of the drug in body fat drops, the concentration in the blood drops. Essentially, the body weans itself off of the drug, preventing major withdrawal symptoms.

In the specific case of THC, which does produce a tolerance after regular use, studies in rats have suggested that the chemical can cause a physical dependence. The rats displayed withdrawal symptoms when treated with a cannabinoid antagonist, a chemical that blocks the action of THC.\textsuperscript{43} However, in practical use a user would not come in contact with an antagonist that acts on the cannabinoid receptors, resulting in a lack of withdrawal symptoms and debate over whether a user is “addicted.”

In addition to the fine line between psychological and physiological dependence, the subject is further complicated by individual body chemistry. Differences in production of neurotransmitters or of receptors on neurons in various areas of the brain make people more or less susceptible to addiction in general. It can also affect how a person’s body reacts to certain drugs. This is why people need various amounts of drugs to get therapeutic benefits (in the case of medicines) or to get high (in the case of drugs of abuse).

To add another twist, tolerance may not necessarily be a sign of abuse. Patients may develop a tolerance to therapeutic drugs, requiring higher doses, while using the drug as prescribed. Furthermore, tolerance – needing more of the
drug to get an effect – does not necessarily cause addiction, nor does addiction necessarily need a build-up of tolerance.

All the distinctions between dependence and tolerance, use and abuse, can seem like a bunch of psychobabble. One can question the practical use of all these definitions, especially when “addictiveness,” as defined by the seeking behaviors of psychological dependence can be applied to everything from nicotine to gambling to running. However, these distinctions can decide everything from treatment for addicts to the level of punishment doled out to those who act outside of the law.

**Xenophobia and Fear: Marijuana**

Prior to the 20th century, medicine was often a shot in the dark. Homeopathic remedies, the old “folk medicine”, relied on toxic substances. However, they were so dilute that there would be hardly any of the active ingredients in any given dose. As organic chemistry progressed, scientists were able to isolate the chemicals in plants which caused the medicinal effects. These plant alkaloids were usually soluble in water, making extraction relatively easy. Opium, from the poppy plant, became ubiquitous not only as the addictive drug smoked in opium dens but as a medicine prescribed for everything from diarrhea to menstrual cramps.

The extraction of marijuana proved more difficult. The active compound, THC, is fat-soluble, making it not readily soluble in water. The THC levels in water- and alcohol-based compositions intended for oral administration could not be easily controlled, and the effects of marijuana-based anesthetics could not be predicted
before administration. Additionally, the effects of THC took longer to take hold than opiates and the doctor would have to wait by the patient to see if his dose had been appropriate. Complications like this caused marijuana to drop out of favor as an anesthetic and the readily available morphine rose in popularity.\textsuperscript{44}

Marijuana is the most widely used illegal recreational drug in the United States.\textsuperscript{45} Despite the presence of the Cannabis plant in the Americas for centuries, smoking marijuana did not become common until the 20\textsuperscript{th} century. Prior to this, cannabis was mostly seen in medicines administered orally, which were unpopular due to their uneven results. The Food and Drug Act of 1906 required that medicines containing marijuana be labeled as such but did not regulate its use. A number of states passed laws in the first three decades of the century, but no federal laws were passed until the Marijuana Tax Act of 1937, which essentially ended the growing of cannabis and hemp by enforcing over-the-top punishments for not paying a one dollar tax for the purchase of marijuana. It wasn't until the 1960's that growing or possessing marijuana became illegal.

Cannabis has a long history of use throughout Southeast Asia, particularly in India. In much of Indian society it was used as a social drug, often smoked or prepared in a drink like a tea. When hemp was introduced to Europe through the Greek and Roman civilizations, it was not regarded as a drug but rather as a crop. Hemp seeds were used as other cereals and the stalks of the plant proved to be unmatched in strength and resistance to rotting, properties important for sea-faring cultures. As the crop moved north, what the people asked of it changed; its
properties changed along with the climate. Even now, varieties of cannabis grown in more northern regions have far lower amounts of the active ingredient, THC, than varieties grown closer to the equator.46

One might wonder what it was that brought marijuana to the forefront in the cultural war of anti-drug legislation. The plant was a source of fiber for fabrics, ropes, and paper, and the majority of North Americans who had heard of hashish weren’t particularly tempted to try it – alcohol, tobacco, and opium were all readily available, and northern varieties of cannabis were not particularly potent.

Early movements that wished to reduce drug legality in the beginning of the 20th century included marijuana, thinking that as other drugs became illegal users would shift to marijuana. Legislation against marijuana seemed pointless because it was such a small percentage of abused drugs. During the first three decades, as drug sales became more and more controlled, marijuana was still available for medical use.

Throughout the 1930’s the influx of Mexican immigrants in the Southwest began to face much discrimination, especially as displaced farmers sought any work as relief from the Great Depression. Marijuana was much more a part of the Mexican culture than the American culture at the time and officials picked up on the drug’s use as a reason to fear the immigrants:

Marihuana, perhaps now the most insidious of our narcotics, is a direct by-product of unrestricted Mexican immigration. Easily grown, it has been asserted that it has recently been planted between rows in a California penitentiary garden. Mexican peddlers have been caught distributing sample marihuana cigarettes to school
children. Bills for our quota against Mexico have been blocked mysteriously in every Congress since the 1924 Quota Act. Our nation has more than enough laborers. (C. M. Goethe of Sacramento in The New York Times, Sept. 15, 1935)\textsuperscript{47}

Fear of the effects of marijuana mixed with xenophobia escalated. Marijuana went from being seen as an innocuous if immoral drug to being the biggest threat to America’s youth. The youth, as they are wont to do, began to experiment with the drug and quickly realized that the effects they experienced weren’t quite what the officials said they were. Marijuana use became much more widespread throughout the fifties and sixties. By 1970 the U.S. Congress made it officially illegal. In 1973, with the creation of the DEA and drug scheduling, marijuana ended up as a Schedule 1 drug: high potential for abuse, no currently accepted medical use in the U.S., and lack of accepted safety for use.

While the government was content to say marijuana had no medical use and leave it at that, scientists continued to probe the usefulness of THC as a medicine. The most successful, well-known of the medicines is dronabinol. Dronabinol is the same compound as the active ingredient THC in the marijuana plant, only prepared in a sesame oil solution as a capsule. This drug, sold as Marinol, is used to treat the nausea from chemotherapy treatments. Dronabinol is listed on the DEA’s Schedule 3 – much less severe than the Schedule 1 of herbal marijuana and with an admitted medical use and less potential for abuse. Dronabinol has some of the same problems as earlier oral preparations of marijuana, namely, inconsistent effects.\textsuperscript{48}
Smoking marijuana is generally not considered a good medical treatment. The dangers inherent with smoking any substance are also present with smoking marijuana. However, inhaling THC gives the users greater ability to titrate the amount of the drug in their system, allowing the drug to better treat their symptoms. THC holds promise as a pain reliever; when combined in treatment with opiates it can act synergistically, requiring a lower dose of both the THC and the opiate (morphine, for example) would required if used alone.\textsuperscript{49} The real trouble with THC research, however, is the stigma attached to it after a century of misinformation. Researchers seeking to develop a treatment from a synthetic cannabinoid, pravadoline, found it had toxic effects on the kidney. Instead of seeking a solution, the company dropped the whole program – “partly for budget reasons and partly to avoid being associated with the image of a cannabis-like drug,” according to Dr. Susan Ward.\textsuperscript{50}

Conclusion

Over the course of the past semester I became aware of just how much we trust our health to people who may not always have our best interests in mind. As a scientist, I’m upset that researchers have to take money from the companies producing the drugs. I’m upset that this money buys the results the companies want – through twisting the researchers’ data or through suppressing the data they don’t want. I’m upset that jaded researchers give in to the companies’ demands.
As a consumer, I'm angry. Drug companies are companies which require profits to reinvest in further developments. However, it is the scale of deception and manipulation that should stir us. The people who run these companies see nothing wrong with pressuring FDA officers to approve drugs without the requisite tests, manipulating doctors into proscribing unnecessary drugs at high dosages, and convincing the public that their drugs are safe and just what they need to feel better.

The question of whether the FDA is doing what it should comes down to the question of what role the government should play in its citizens' lives. I'm not a scholar of politics and government; I can only give the perspective of a citizen and a student of chemistry. The current incarnation of the Food and Drug Administration intends to keep citizens' safe. The majority of the people working there go in day after day with that in mind. It is a select few that deliberately ignore the rules to get unsafe drugs approved.

There is no way to remove politics from a political group. What needs to happen is not a restructuring of government, or a change in the way drugs are approved, or a new way of appointing an administration head. What is needed is transparency. Honesty and straightforwardness in the long run will help not only the FDA but the companies. Medicines that are dangerous but, for people who have no other option, effective should be labeled and marketed as such and available for those who, after careful consideration of all the facts with their doctor, decide it is the best route. Attempting to market one drug as the answer for everyone along
with mistakes like Vioxx make the public wary while making them feel more dependent on drugs than ever.

The DEA also plays an important if sometimes overbearing role. There are a number of dangerous drugs becoming more widespread; methamphetamine, for example, and its derivatives that are increasingly more dangerous and harder to detect, or misuse of prescription drugs. The DEA is a necessary part of stopping the spread of dangerous drugs like this. However, fear and misunderstanding can overtake science or public sentiment when the black and white of law enforcement meets the gray of daily life.

I'm not suggesting that marijuana be made legal. There are a number of reasons for it remaining a controlled drug. I am more concerned that the stigma surrounding the plant is holding back steps that could lead to the development of better drugs for conditions that currently are a part of the “medical marijuana” debate. The government has already conceded that the compound has a medical use; it is the image of reefer madness that is keeping the plant on the first schedule, not its actual attributes.

Overall, the United States has a system in place to protect its citizens. For the most part, this system works. However, it falls to us each individually to remain aware, to protect our own bodies, and to seek to be informed about what we are putting inside our bodies.
NOTES

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5 Ibid
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25 Ibid p 197
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46 Iversen pp 4-14
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49 Ibid p 70
50 Ibid p 41