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Thinking Outside The Black Box: Current Policies and Problems With the FDA's Highest Drug Safety Warning

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Thinking Outside The Black Box
Current Policies and Problems With the FDA’s Highest Drug Safety Warning

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Kylene Halloran
2009
Based on data collected from clinical trials and post-approval surveillance systems, the Food and Drug Administration (FDA) issues warnings to communicate increasingly dangerous and/or preventable risks to doctors and their patients. The black box warning, the highest of all warnings issued by the FDA, emphasizes risks the FDA has deemed are critical to safe use of the drug. The warning has numerous implications for the pharmaceutical companies and physicians. The purpose of this thesis is to discuss the infrastructure of the adverse effect detection system, the effects of the Food and Drug Amendments Act (FDAAA) of 2007, and the need for FDA to reevaluate the black box warning system.

Recent studies and public scandals have demonstrated the warning system is flawed, from the information on which FDA drug safety advisory committees base their decisions to the methods by which they communicate their findings. Most critically, the warnings often go unheeded by doctors due to inconsistencies in the warning system, and the language and methods by which this information is communicated.

The FDAAA of 2007 addresses many of these underlying issues. Mending these dysfunctional systems will undoubtedly strengthen the advisory committee’s ability to properly assess safety issues. However, even if data gathering systems are perfected, doctors most likely will not abide by an inconsistent warning system that inflates or downgrades safety information. Only when the warnings accurately reflect the risk-benefit profile of a medication will healthcare providers regain trust in the FDA’s ability to identify, label and communicate these issues.
Acknowledgements

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INTRODUCTION

Over the last 100 years, the Food and Drug Administration (FDA) has developed from a one-person office with little regulatory power in a sea of fraudulent “patent medications” into a department with global responsibilities, a rigorous drug approval process, and significant control over a major segment of the United States economy.¹ (1) In contrast to popular belief, a “seal of approval” from the FDA does not indicate the drug is without risk. All medications have side effects, some more serious than others. The FDA’s website states, “At the heart of all FDA’s regulatory activities is a judgment about whether a new product’s benefit to users will outweigh its risks.” (2) The FDA receives its safety information from numerous sources, including premarketing clinical trial data, and post-approval surveillance systems. Based on these data, the FDA requires pharmaceutical companies to list all of the drug’s side effects on its labeling, and uses various visual methods to communicate increasingly dangerous and preventable risks to doctors and their patients. The black box warning, the highest of all warnings issued by the FDA, highlights serious side effects the FDA has deemed are critical to safe use of the drug. The issuance of a black box warning has numerous implications for the pharmaceutical companies and physicians.

Theoretically, the warning system is the perfect way to provide access to the most effective treatments while maintaining patient safety. Realistically, the warning system is flawed, from the information on which FDA drug advisory committees base their decisions to the methods in which they communicate their findings. The lack of complete premarket clinical trial data and inadequate post-approval monitoring systems force

¹ Overseeing the regulation of items accounting for 25 cents of every dollar spent by consumers in the United States. (3)
committees to make decisions based on case reports or flawed analyses. (4) The nonspecific, and arguably unscientific method by which a drug receives a black box warning, in addition to biases of committee members making critical decisions regarding the fate of dangerous drugs, have cast doubt on the quality of the system. (5) Most critically, the warnings often go unheeded by doctors due to inconsistencies in the warning system, and the language and methods by which this information is communicated. (6) Rather than a warning system that fully informs and maintains safety, doctors are prescribing medications based on incomplete and biased black box warnings, leading to unexpected adverse events. (7)

Recently, the FDA has undertaken a major campaign to revitalize and restructure based on recommendations by the Institute of Medicine (IOM) Report published in 2006. (8) Many of the recommended changes address issues with the foundation of the warning system, including completeness of clinical trial data and the inadequacies of the post-approval surveillance system. Repairing these systems will undoubtedly strengthen the drug safety advisory committee’s ability to properly assess safety issues. However, even if data gathering systems are perfected, doctors will not abide by an inconsistent warning system that inflates or downgrades safety information. (7) Newfound authority and monetary support granted through the 2007 FDAAA has given the FDA the ability to revolutionize their approach to drug safety and address the concerns regarding post-approval drug warnings.

The purpose of this thesis is to assess the potential impact that the changes initiated by the FDAAA may have on the addressing the flaws of the drug warning process. To do this, I will first discuss the present infrastructure of the adverse effect
detection system, and the FDA’s ability to respond in a timely, coherent manner.

Secondly, I will examine the effects of the FDAAA of 2007 to determine how it will potentially improve this process. Finally, I will demonstrate that in order for the black box warning system to be effective in conveying the importance of associated risks, the FDA must reevaluate all black box warnings, eliminate or revise those that are outdated or no longer necessary; and reword the warnings to more concisely communicate critical safety information.

**METHODS**

A review of several websites and texts provided much of the early history of the FDA, including the websites the History of the Center for Drug Evaluation and Research (CDER), the History of the FDA, and the book *Inside the FDA*. (1, 9, 10) Recent major events in the FDA (1970- current) were identified through a review of all *New York Times* articles during this time period pertaining to the FDA, and the news releases provided on the FDA website.

A systematic review using the Scopus search engine with the key words “Food and Drug Administration,” “Black Box Warning,” and “Labeling” identified review articles of interest detailing FDA policy and major legislation. Books such as *Powerful Medicines*, *The Truth About Drug Companies: How They Deceive Us and What to do About It*, and *Global Pharmaceuticals: Ethics, Markets, and Practices* helped identify problems with the warning systems. (11-15) The recent Guidelines and press releases found through searches on the FDA website using key words such as “FDAAA,”
“PDUFA IV,” “The Sentinel Initiative” and “The AERS system” further detailed these issues and described the proposed solutions through the new legislation. (16)

Examination of *Physicians Desk References* (PDR) beginning in 1979, and searching backwards in time revealed the earliest drug to receive a black box warning. (17-22) Searches of black box warnings on the Formweb website, and the *Physicians Desk Reference* from 2009 provided the current information on the warnings. (22, 23)

Finally, personal communication with industry experts regarding information unavailable through the FDA website or published literature completed my research. (Dr. Bryan Liang, M.D., J.D., Ph.D. in public policy, is a professor at the Health Law Studies at California Western School of Law, and is on the editorial board of the *Journal of Clinical Anesthesia*. Dr. Louis Morris, Ph.D., served as acting director of the Division of Drug Marketing, Advertising, and Communication (DDMAC), specializing in patient package inserts (PPI’s) and label formatting. Joyce Generali, M.S., R.Ph, is Director of the Drug and Information Center at Kansas University Medical Center and creator of the FormWeb: Black Box Warnings website. (23) Dr. Mary Kremzner, Pharm. D., works in the Center of Drug Evaluation and Research, Division of Drug information. Dr. Jean Cunningham is a fellow under Dr. Kremzner. Dr. Dr. John Swann, Ph.D. is an historian at the FDA History Office. Ms Cindy Lachin is a research assistant at the FDA History Office, and provided the pictures available at the conclusion of the thesis. Ms. Lynn Sette is library liaison at Yale School of Medicine.)
PART I: THE HISTORY OF THE FDA

1862  Creation of Department of Agriculture
1906  Pure Food & Drug Act
1937  The Federal Food, Drug & Cosmetic Act
1951  Durham Humphrey Act
1955  Medwatch Pilot Study
1962  Kefauver-Harris Amendment
1964  1st Boxed Warning on Chloramphenicol
1966  Drug Efficacy Study Implementation project & Fair Packaging and Labeling Act
1971  National Drug Experience Reporting System
1979  Black Box Warning Codified
1992  Prescription Drug User Fee Act
1997  FDA Modernization Act
2003  Medicare Prescription Bill
2006  New Package Requirements & Institute of Medicine report
2007  FDA Amendments Act
2008  Sentinel Initiative
When the FDA was originally established, it did not have the ability to require testing, establish labeling standards, or remove drugs from the market even if they were dangerous to public health. The FDA acquired the authority to regulate drugs through several key laws in response to major public health disasters involving the drug industry, typically those that resulted in the deaths of several hundred patients. Because of this authority, the United States FDA set the international standard for safety monitoring and innovation during most of the 20th century. Massive budget cuts in the 1980’s, at a time when the pharmaceutical industry and technology was growing exponentially, prevented the FDA from developing new, more effective safety monitoring tools, and stalled innovation within the agency. Growing responsibilities abroad at the turn of the 20th century highlighted these weaknesses. In response to growing public distrust, Congress passed the FDAAA of 2007, granting the FDA more authority, but requiring a more transparent, modernized administration. (24)

The Chaos of Medicine in the 19th Century

In the 1800’s drugs need not be safe, or effective. One could bottle water and advertise it as a cure for dementia, cancer, impotence, or any number of ailments. And this “medicine” likely would have been safer than most elixirs on the market. By the mid 19th century, there existed more than 600 “patent medications” all claiming to alleviate some form of human suffering. (10) Most of these medications did not accomplish what they claimed, and many caused serious side effects.

In 1820, disturbed by the general lack of suitable information available on these “drugs,” eleven physicians sought to differentiate which medications were effective from
those that were hoaxes. (Fig. 1) This group compiled the 217 drugs that they deemed to be worthy of use and published them in the first *United States Pharmacopoeia* (USP). (25)

Despite their efforts, the world of patent medications continued to flourish throughout the 1900’s. By the turn of the century ads for patent medications accounted for almost half of newspapers’ advertising income, a sign that the public continued to use these “medications,” no matter how ridiculous their claims may have been. (26) For example, in an 1887 advertisement, the makers of *Mrs. Winslow’s Soothing Syrup* claimed:

For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle. (Fig 2) (27)

This advertisement appeared despite articles published by physicians in the *Lancet* reporting that the use of the syrup caused respiratory depression and death. 2 (28)

**1862: The Birth of the FDA**

The political roots of the FDA were established by the creation of the Department of Agriculture in 1862 by Abraham Lincoln in the midst of the civil war. However, the Department had no real authority, allowing the food, drug, biologic and cosmetic industries to operate without repercussions. Various forms of food and drug testing were conducted over the next twenty years without much benefit to the public. Eventually a new division, the Department of Chemistry, was established in 1883 with Dr. Harvey W. Wiley as its leader. In addition to testing patent medicines, Wiley created the “Poison

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2 Use of opioids, including morphine, can also cause constipation- the reason most doctors prescribe stool softeners for patients taking the medication. Therefore, the claim of “bowel regulation” was erroneous.
Squad” composed of young, healthy men who were given food contaminated with increasing amounts of preservatives in order to monitor side effects.\(^3\) (Fig. 3) (1) The shocking results motivated Dr. Wiley to pursue restrictions over the food and drug industries during the next two decades.

1902-1934: The Birth of the Label

Despite Wiley’s valiant efforts, it would take two public relations catastrophes, one generated by a muckraking journalist and the other originating from an author attempting to promote socialism, before Congress would attempt regulatory legislation on the food and drug industries. The first was Samuel Hopkins Adams’ 1905 publication of an 11 articles series entitled “The Great American Fraud,” that sought to expose the world of patent medications. Descriptive section titles included “The Subtle Poisons,” “Preying on Incurables,” and “The Fundamental Fakes.” (29) Adams brusquely attacked the patent medication industry through passages such as,

> Gullible America will spend this year some seventy-five millions of dollars in the purchase of patent medicines. In consideration of this sum it will swallow huge quantities of alcohol, an appalling amount of opiates and narcotics, a wide assortment of varied drugs ranging from powerful and dangerous heart depressants to insidious liver stimulants; and, far in excess of all other ingredients, undiluted fraud. (29)

In 1905, Adams was invited as a guest of honor to the New York State Medical Association dinner, in the company of luminaries such as Dr. William Mayo, President of the American Medical Association (AMA). Adams’ speech criticized newspapers for publishing patent medicine advertisements, accusing the papers of “willfully injuring the health of the public.”(30)

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\(^3\) The poison squad ingested megadoses of borax (a component in detergents), salicylic acid (a drug used to treat acne because it causes the epidermis to shed more rapidly, preventing pores from clogging), formaldehyde (used to preserve corpses), and sulphuric acid (used to manufacture fertilizer). Wiley was mostly concerned with the buildup of these chemicals over the long-term.
The second public relations disaster came one year later, when Upton Sinclair published his book *The Jungle*, detailing the life of a slaughterhouse worker. (31) Sinclair had intended to expose the world of “industrial masters” and their “wage-slaves,” but the public, instead, focused on the horrors revealed about food products generated by the meat industry. (32) An infamous passage informed readers of the unintended ingredients of Durham’s Pure Leaf Lard: the unlucky workers who fell into open vats. (10)

Public outcry fomented by both publications, in addition to support from President Theodore Roosevelt, led to the 1906 *Pure Food and Drugs Act*, which introduced new food and drug laws aimed at providing consumers with information in the form of labels. (33) The law prohibited labels from being false or misleading, and required that certain substances including alcohol, heroin and cocaine be listed on the label. Additionally, in the case of drugs, variations from *US Pharmacopeia* standards of strength, quality and purity had to be documented. (34) The law, however, neglected to mention advertisements and other forms of promotional material.

Furthermore, the Supreme Court dealt an additional blow to the already weak law in 1911 when it ruled in favor of a known patent medication: *Dr. Johnson’s Mild Combination Treatment for Cancer*. The ruling stated that false claims of efficacy, even on the bottle label, were not illegal. The new law only forbade misleading statements regarding ingredients or the identity of the drug."(34)

The *Sherley Amendment* in 1912 attempted to close this loophole by prohibiting the “labeling of medicines with false therapeutic claims intended to defraud the purchaser.”(34) The FDA quickly discovered intent was nearly impossible to prove in
court, rendering the amendment useless. Thus, the agency needed to find new legal tools to regulate the food and drug industries.

1934-1960: Safety Requirements and the Creation of Post-market Surveillance

Dinitrophenol, a commonly used diet drug in the early 1930’s, was found to work by disabling the electron transport chain in the mitochondrion, allowing energy to escape the body as heat. In higher doses, it also raises the body’s core temperature to levels that denatures proteins and causes brain damage. (Fig. 4) In 1933 and 1934, doctors investigating the deaths of patients who suffered from hyperthermia made this connection. (35) By 1935, newspapers began reporting a correlation between use of dinitrophenol and the development of cataracts, employing sensational titles such as “Anti-fat Users Blinded.” (36) Despite numerous case reports of adverse events and negative publicity, the Office of Drug Control could not order the manufacturer to withdraw from the market. Prosecutions in 1936 and 1938 by the FDA charged the drug manufacturer with false and fraudulent statements regarding safety, yet resulted only in the seizure of 26 bottles of “Slim” and a court imposed fine of $50.00 for another dinitrocrestol formulation. This mild punishment was not enough to make manufacturers stop selling the drug. (38)

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4 To prove intent one must demonstrate by clear and convincing evidence that a statement was false, that the false statement was material, and that the injured party relied on the false statement.

5 This represents only three shipments- two seized in Pittsburgh, Pennsylvania, and one Fort Wayne, Indiana. They were seized because the bottle claimed the pills were “safe to use” despite popular medical opinion to the contrary. (37)
However, the FDA had no jurisdiction over properly labeled formulations. Thus, the FDA was restricted to issuing warnings in the form of press releases about the harmful side effects of the drug, even though the compound, previously used as a yellow food dye at the turn of the century, was banned when Wiley and his colleagues discovered its toxic effects in 1907. (Fig.5) (38) However, because dinitrophenol was no longer being used as a coloring agent, but as an active drug, this law did not grant the FDA authority over its use.

In 1937, the FDA faced another dilemma, when reports of unexpected deaths resulting from renal failure in Tulsa, Oklahoma were traced to a new formulation of sulfanilamide, an antibiotic used to treat illnesses as varied as gonorrhea, sore throat, ear infections, soft-tissue infection and syphilis. (39) In an attempt to create a liquid form of the drug, the S.E. Massengill Company’s chief chemist mixed sulfanilamide with diethylene glycol. The deadly combination killed 105 patients, including 34 children. (39) Again, the FDA had no authority to recall a drug based on issues of patient safety. Accidentally, the chief chemist dubbed the new formulation an “elixir,” implying that it contained alcohol when it did not, allowing the FDA to seize the product based on the 1906 labeling laws. Secretary of Agriculture Henry Wallace reported, “Had the product been called a ‘solution’ rather than an ‘elixir’ no charge of violating the law could have been brought.” (40) In his report he stated that relatively simple animal studies could have easily revealed the toxicity of the new formulation, and urged for stronger legislation to prevent future deaths.

This public disaster, dubbed the “Massengill Massacre” gave Senator Royal S. Copeland the public support required to introduce a new bill on December 1, 1937. The
Federal Food, Drug and Cosmetic Act required manufacturers to provide scientific proof of safety and submit this data to the FDA in order to receive the FDA’s approval before it could begin marketing a new drug. (41) Thus, the New Drug Application was born. (9)

The legislation also authorized the FDA to inspect factories, eliminated the Sherley Amendment’s requirement to prove intent to defraud, and allowed the FDA to designate which drugs could not be safely labeled for over-the-counter consumption (OTC), thus necessitating a prescription from a health care professional. Though the FDA could not require the pharmaceutical company to classify the drug as prescription only, they did have the ability to remove the product and sue the manufacturer for misbranding if the FDA disagreed with the OTC designation. This legally gray-area was clarified by the Durham-Humphrey Act of 1951, which authorized the FDA to classify the drugs, rather than placing the responsibility on the pharmaceutical manufacturers. (42)

In addition to creating pre-marketing drug safety measures in the mid 19th century, the FDA initiated post-approval safety monitoring systems. A pilot study in 1955, focusing on adverse drug reactions reported by hospitals and pharmacists eventually developed into a voluntary reporting system with nearly 200 hospitals participating in post market evaluation of new drugs. (1) This system served as the main forum for post-market surveillance and the basis for issuing recalls and warnings regarding drug safety. This pilot study was an early version of the current Medwatch System.
1960-1966: Requiring Efficacy and a Tarnish on the Pharmaceutical Industry Image

In the late 1950’s Senator Kefauver from Tennessee, known for highly publicized hearings on organized crime, found a new target: pharmaceutical companies. His committee hearings on the pharmaceutical industry made newspaper headlines, exposing massive price inflation and tarnishing the public’s perception of the industry. (Fig. 6) Senator Kefauver argued convincingly for lower drug prices, proof of efficacy as well as safety, and greater restrictions on direct to consumer advertising. Though strong lobbying influences in Congress and a lack of White House support stalled the legislation, the aftermath of a pharmaceutical scandal in Europe would soon reinforce Kefauver’s portrait of the greedy pharmaceutical industry.

In 1960, Richardson-Merrell submitted a New Drug Application for thalidomide, an anti-emetic widely used in Europe to ease nausea in pregnant women. Dr. Frances Oldham Kelsey reviewed the application and refused to approve the drug until the company could provide better safety data, specifically regarding birth defects. Later that year, reports of phocomelia, a rare birth defect resulting in flipper-like appendages, began to surface in Europe. By 1962 10,000 cases of birth defects were reported in Europe and Africa. Kelsey was heralded as a hero and presented the President’s Award for Distinguished Federal Civilian Service in 1962.

As a result of this disaster, drug companies were subjected to intense scrutiny under the Kefauver-Harris Amendment of 1962. (43) The Act stated that drugs must be proven both safe and effective using adequate and well-controlled scientific studies.\(^{(10)}\) The law also required drug companies to report all adverse reactions to the FDA, that

\(^{6}\) The FDA hired statisticians in 1970 who recommended organized, double blinded, randomized, placebo controlled, dose response studies.\(^{(10)}\) This was in stark contrast to previous methods, which essentially equated to trial and error.
they include a complete discussion of a product’s risks in direct to consumer advertising, and added structure to the practice of human trials. Always one to have the last word, Kefauver included a provision allowing companies to produce generic versions of off-patent drugs, which would eventually drive down the cost of medicines. (44)

In 1966 the FDA and the National Academy of Sciences launched the Drug Efficacy Study Implementation (DESI), which evaluated more than 3000 products and over 16,000 therapeutic claims. Many drugs received a “DESI box” in the Physicians’ Desk Reference, stating their product may not be effective. (20) By 1984 nearly 1/3 of the products evaluated were found to be ineffective and removed from the market. (1)

1966-1982: Advances in Communication and New Labeling requirements

Over the next two decades, the FDA focused on greater consumer awareness through informative labeling and advances in communication. In addition to the DESI project, Congress passed the Fair Packaging and Labeling Act of 1966, which required pharmaceutical companies to report the identity of the product, manufacturer, packer or distributor and the net quantity of drug on the product label. (45) In 1968, under the authority granted by the Fair Packaging and Labeling Act, the FDA mandated a two-sentence warning on the container of isoproteronol inhalers that cautioned patients against overuse. This was technically the first patient package insert (PPI). Two years later, the controversy over birth control pills allowed the FDA to flex its authoritative muscle by requiring a PPI, detailing their proper use as well as serious side effects.

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7 This boxed information should not be confused with a boxed warning. The DESI box was meant to convey a lack of scientific information regarding efficacy. The boxed warning, officially codified in 1979, but used as early as 1964 is a designation of important drug safety information.
In addition to adjusting the content of the label, the FDA created a standard format for all labeling information in order to best communicate pertinent information to healthcare practitioners and patients. Prior to the 1979 regulations passed by the FDA, drug companies submitted information to *The Physicians’ Desk Reference* in any format they deemed appropriate. Federal code 201.56 and 201.57 established requirements for the headings and content of prescription drug labeling in *The Physicians’ Desk Reference* as well as in PPI’s. Now, all drugs would be subject to the same format and require the same type of information. The legislation also included a section regarding a “prominently displayed box” for the most crucial information. *The Black Box Warning System* was born, a subject that will be explored in the later sections of the thesis.

During the 1970’s the FDA also tried to reach out to doctors, increasing communication through two initiatives: *The FDA Drug Bulletin* and *The National Drug Experience Reporting System*. The bulletin was an effort to update doctors on recent labeling changes or drug safety issues. It covered topics such as the dangers of diethylstilbestrol use during pregnancy as well as prescription of drugs for unapproved purposes. By 1984 the FDA launched the electronic bulletin board in order to promote widespread, rapid distribution of warnings.

*The National Drug Experience Reporting System* was established in 1971 by the National Academy of Sciences. Previously, the FDA had simply collected all adverse reaction reports from various sources, including doctors, manufacturers and patients. They now had the job of cataloguing, storing and disseminating the information to

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8 *The Physicians’ Desk Reference* is essentially a collection of package inserts published by Thomson Reuters. Pharmaceutical companies pay a fee to include their drug in the text, allowing it to be distributed to physicians free of charge. Many drugs, including generics or drugs produces by smaller firms are not included in the text. Physicians have recently described it as a “paid advertisement by the pharmacologic company and approved by the FDA.”
physicians. This system was the first version of the current *Adverse Event Reporting System (AERS)*. (47)

**1983-1990: Budget cuts, AIDS and Speedy Drug Approvals**

The momentum generated by the Kefauver-Harris Amendment quickly dissipated with the election of Congressional representatives that favored industry interests, and massive downsizing of the agency. Elected in 1981, President Ronald Reagan’s platform was centered on smaller government and lower taxes. He kept his promise by cutting nearly 10% of the FDA staff at a time when the number of drugs, and therefore responsibilities were expanding. He also promptly fired the commissioner, Jere Goyan, because he did not align with party interests. According to Fran Hawthorne, author of *Inside the FDA*, “Several FDA initiatives to give consumers more information about the side effects of drugs and the ingredients in packaged food were stopped cold, and even enforcement actions were halted mid-investigation.” (10)

Worse yet, a generic drug scandal tarnished the image of the FDA. Inquiries in 1989 regarding how the FDA handled generic drug applications revealed several FDA officials accepting bribes for faster drug approvals. (48) Five FDA officials were convicted of felonies.

In 1981 the Centers for Disease Control received reports from Los Angeles of young men with fatal infections of *Pneumocystis carinii*, as well as a particularly virulent form of Kaposi’s sarcoma. This constellation of diseases is normally observed in patients with long-term illnesses like cancer or those taking immunosuppressive medication to

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9 Almost every new President would replicate this action, effectively weakening the system by preventing each commissioner from serving more than 4 years. Some served only a few months.
avoid transplant rejection. French Scientist Luc Montagnier discovered a retrovirus in 1983, which was later renamed human immunodeficiency virus (HIV). However, little was known about its dissemination and treatment. By 1990 the death toll reached over 100,000 in the United States. (49) Pharmaceutical companies saw little profit in finding a cure for HIV or rare diseases, and growing anger was directed at the FDA for stalling the few drug options they offered.

In response, a series of laws designed to encourage research for less profitable illnesses, and speed approval times for drugs aimed at treating debilitating illnesses with few available therapeutic options were passed throughout the 1980’s. The Orphan Drug Act of 1983 encouraged the manufacture of drugs for rare diseases, and the 1984 Hatch-Waxman Act created the abbreviated new drug application for generic drugs, eliminating expensive patient trials required for drug approval. (50, 51) In 1985 and 1988, the FDA created the compassionate use and the treatment investigational new drug applications, respectively. The prioritized applications allowed drugs to reach fatally ill patients in a timelier manner.


In the wake of massive budget cuts, the new FDA commissioner Dr. David Kessler looked for different ways to fund his agency. The Prescription Drug User Fee Act of 1992 (PDUFA) provided the money Kessler sought by requiring a fee for new drug applications from the pharmaceutical companies. (52) However, the funding came with strings attached: the financial support could only be used for drug approval, and decisions regarding the drug application were subject to deadlines. All other tasks had to be funded
by the federal government, including post-market surveillance, a system under attack from experts in the epidemiology field.

The FDA of the 1990’s is famous for its attack on the tobacco industry. The agency devoted much of its time and energy to regulating all tobacco products. Kessler’s “tobacco team” consisted of 89 full time staff members. (10)

In comparison, an article in the New York Times in October of 1997 revealed that the drug surveillance division was comprised of only 55 full time staff members with the mammoth task of monitoring all post-market adverse drug effects. (53) The user fees generated $36 million for the FDA, but under the 1992 PDUFA legislation, none of that money could go towards post-market surveillance. The FDA allotted only $140,000 towards MedWatch, the main system for reporting and disseminating information about adverse effects. (53) By the late 1990’s, experts such as Dr. Murray Lumpkin, deputy director of the FDA’s Center for Drug Evaluation and Research (CDER) was encouraging the FDA to use large health databases in a more organized, consistent manner to evaluate postmarket issues. (53) However, it would be nearly a decade before Congress and the FDA would respond.

In response to Kessler’s efforts to regulate the tobacco industry, a conservative Congress tried to diminish the FDA’s capacity to regulate pharmaceuticals, by allowing certified private agencies to review new drug applications in order to speed drug approvals. (10) A fierce defense from Kessler prevented the 1997 FDA Modernization Act (FDAMA) from including this provision, but the renewed PDUFA further decreased the time allotted for new drug review. (54) Critics worried that shorter review times would lead to unwarranted drug approvals, a fear validated when twelve previously
approved drugs were recalled in the late 1990’s. (10) FDA staff argued that the percentage of new drugs withdrawn remained stable, and some of the drugs were approved well before the 1992 legislation, thus the speedier review processes were still effective. (55)

1997-2004: Globalization and Creative marketing

Despite initiatives by Kessler to modernize the FDA, the agency could not meet the demands of an increasingly global economy. For example, sparse resources led to the inspection of only 1/3 of foreign companies shipping chemicals to the United States. Of those inspected, official action against 32 foreign companies was recommended, then later downgraded to lesser violations that did not require a return trip for re-inspection. (56) In 2002, the FDA inspected only 1600 plants, down from 4300 in 1980. (57) In 1997 Kessler admitted, “We built a system back 100 years ago that served us very well for a world within our borders. We didn’t build a system for the global marketplace.” (58)

The FDA also had issues at home. More relaxed direct to consumer (DTC) advertising laws passed in 1997 emboldened the pharmaceutical industry to spend huge sums of money promoting its products, especially when attempting to combat criticism within the medical community. (59) From 1997 to 2005, industry spending grew by 20% per year and focused on the “blockbuster” drugs treating hyperlipidemia, asthma and allergies. (59) The agency issued on average 10 warning letters per month from 1997 to 2000 regarding “misleading promotions.” (60)

10 In response to the ALLHAT study performed on Pfizer’s new drug Cardura (doxazosin mesylate) in 2001 stating an increased risk of CHF and cardiovascular disease and decreased efficacy in comparison to a diuretic, the company increased funding towards marketing rather than conducting their own study, and refused encouragement to notify doctors and patients using the drug. The strategy worked. Sales were largely unaffected.
To evade what regulations were in place, pharmaceutical companies became more creative in their advertising campaigns. Companies such as Intermune sponsored dinners with “expert reporting” on off-label uses for their drug. They also founded nonprofit patient advocacy groups to “inform” patients of the off-label uses. (61) Most disturbingly, a report by Dr. Thomas Bodenheimer in 2000 in the New England Journal of Medicine (NEJM) revealed the pharmaceutical industry had corrupted an area once thought to be sacred: the peer-edited journal. Bodenheimer reported that industry may be influencing data generated in clinical trials. Additionally, major medical journals, the primary source of information for off-label prescribing, were publishing articles written by public relations’ firms under the guise of authorship by well respected authorities paid to sign their names as authors in exchange for “consulting fees.”(14, 62)

Pharmaceutical lobbying reached the apex of its power in the adoption of a provision in the Medicare Prescription Bill in 2003. (63) Congress expressly forbade Medicare to negotiate with pharmaceutical companies for competitive prices. To negotiate lower drug prices for their patients, competitive bidding is an integral part of the procurement process for such governmental departments as the Department of Defense and Veterans Affairs as well as large health maintenance organizations. Now the government had little bargaining power to influence prescription cost for our senior citizens.

2004-Present: Labeling Changes, The IOM Report, and a “Lifecycle” Approach

In the late 1990’s, side effects from two well known and highly prescribed classes of drugs, COX-2 inhibitors and antidepressants, began to generate media attention. Cover-ups and deception by the pharmaceutical industry generated public outrage. These
feelings were magnified by accusations from FDA officials of suppression of data by their superiors. Dr. Andy Mosholder, an FDA drug safety researcher had combined data from several antidepressant clinical trials and found evidence of increased suicidal ideation. However, in the 2004 advisory panel, Dr. Mosholder’s superiors suppressed parts of his report, arguing his results were inconclusive. (64) A placebo-controlled trial conducted by Columbia University a year later reinforced Mosholder’s data. (11)

The public’s concerns were further validated in 2004, when Dr. David Graham, an FDA drug safety researcher, testified at a Senate Finance Committee hearing that the FDA was no longer capable of protecting citizens from drug safety crises. Graham stated that he was criticized for reporting adverse effects of approved drugs to superiors, and that pharmaceutical interests trumped concerns of public health. (65) Both the Vioxx (rofecoxib) and antidepressant scandals appeared to support his claim.

Though tension over these public scandals was mounting, the FDA focused on another issue: drug labeling. In the 1980’s the FDA acknowledged that labeling geared towards doctors had become so lengthy and complicated, (termed “linguistic toxicity” by Avorn and Shrank), that practitioners had difficulty finding important information. (3) To simplify complicated labels, the FDA created a new template for drug information to be applied to all drugs approved after 2001. Drugs approved before 2001 could elect to reformat their package insert to comply with the new standard. (3)

While the FDA focused on labeling, issues with imported drugs escalated, revealing problems with manufacturing plant inspections and the ability of the FDA to track problematic drugs to its source. In 2007, a Chinese factory that typically produces glycerin, a product used in several products such as toothpaste, actually exported
diethylene glycol, the substance that caused the 1934 sulfanilamide disaster. By the time the FDA located the manufacturer, the plant was closed and the Chinese companies denied responsibility. (66) In 2008, nineteen patients died and 785 suffered complications from heparin imported from a Chinese factory that had not been inspected by Chinese or American officials. (67) Baxter International, the distributor of the drug, found the contaminant through advanced chemical testing. According to the Baxter website the presence of a remarkably heparin-like compound was introduced, “…in what appears to be a deliberate scheme to adulterate a life-saving medication.” (68) The motive was unknown, though many speculated it was to cut costs.

Drug withdrawals, issues involving the globalization of drug manufacture, and problems within the administration (brought to public attention with the Vioxx and antidepressant hearings) prompted the deputy commissioner of the FDA, Dr. Janet Woodcock to admit that the drug safety system had broken down. This admission prompted a review of the FDA safety protocols and policies by the Institute of Medicine. (8, 69)

The 2007 report included a recommendation to change in the FDA’s attitude towards drug safety. Previously, emphasis was placed on halting dangerous drugs from entering the market through the approval process. However, many serious side effects, especially those that are rare or result after years of use, went unaddressed for months or years. The IOM recommended a “lifecycle” approach, with an emphasis on addressing drug safety both before and after drug approval. This required enhancing the post-market surveillance systems and creating better communication between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE). The report also
included recommendations regarding conflicts of interest, direct to consumer advertising, and the agency’s research capacity. (8)

In May of 2007, Congress responded with the *FDA Amendments Act* (FDAAA), providing the FDA with the necessary funding and authority to carry out the recommendations of the IOM. The legislation granted the FDA the authority to issue monetary penalties for failure to comply with post-market studies, labeling changes or restrictions, as well as failure to post clinical trials on an FDA website. The legislation also required the FDA to develop rigorous safety performance measures and provide implementation details on a web site to improve transparency and communication. The FDA continues to respond to the report, listing their accomplishments to date on their website “FDAAA Implementation- Highlights One Year After Enactment.”(70)
PART II: THE WARNING SYSTEM
Reporting and Surveillance: Pre-market and Post-approval Systems

The FDA monitors a drug throughout its “lifecycle,” before and after approval, in order to detect and evaluate risks associated with a medication. As discussed in the previous section, the FDA’s authority over pre-market approval increased greatly in 1937 with the Federal Food, Drug and Cosmetics Act, as well as the 1962 Kefauver-Harris Amendment. In order to pass the rigorous New Drug Application standards instituted by the FDA, a company must complete patient trials to investigate toxicity, efficacy, pharmacodynamics and pharmacokinetics, under the trial guidelines established by the FDA in 1970, and revised in 1985. (10) These “phases” are typically conducted on several hundred participants over weeks or months. The pre-market approval process came under severe criticism in the 1980’s and 1990’s, first for being too slow and meticulous, then after the passage of PDUFA in 1992, for being too quick and sloppy. Additional issues included “generalizability” of clinical trial patient populations, and ownership over clinical trial data. These issues are explored in the next section.

The need to monitor the second half of a drug’s “lifecycle” was recognized in 1955 when the FDA instituted the adverse reaction reporting system. (1) A study related to cancer drugs in 2003 found that adverse reactions may be discovered a long as 36 years after FDA approval. (71) Prior to the 2007 FDAAA, the administration used three methods of post-market surveillance to identify or further investigate adverse reactions: Phase IV clinical trials, Medwatch, and the Adverse Event Reporting System (AERS) database. Phase IV clinical trials are post approval studies used to detect rare or long-term adverse effects over years, rather than weeks to months, and with a larger patient population than phase II-III studies. Though randomized, prospective, placebo
controlled, double-blind clinical trials are the “gold standard,” they are expensive, time consuming, cannot detect very rare adverse effects, and cannot follow patients indefinitely for adverse effects that may occur after decades of use. More importantly, they not reflect ‘real world use’; this even suggests more strongly the need for post-market surveillance.

*Medwatch* is a voluntary reporting system that receives information from a variety of sources, including pharmacists, nurses, physicians, and patients. Its purpose is to identify possible adverse drug effects once a medication is on the market. The program was officially established in 1977 as the *Drug Product Problem Reporting System*. In 1988 the Administration divided the system into two parts, creating the *Drug Quality Reporting System* and the *USP Drug Product Problem Reporting Program*. In 1993 the program was renamed for a final time to *Medwatch*. In 2007, the FDA received 486,882 adverse event reports. (72) The Administration estimates that only one out of every ten adverse events is reported. (73) Medwatch is also a method of communicating to health professionals, institutions and the public through email notifications. (74)

The *Adverse Event Reporting System* (AERS), formerly known as the *Spontaneous Reporting System* and the *National Drug Experience Reporting System* is a database of adverse events. The database combines the voluntary *Medwatch* adverse event reports with mandatory pharmaceutical company reports. Pharmaceutical companies are required to report adverse events, found either through clinical trials or reported to the drug company from healthcare professionals, to the FDA within 15 days. (75) If a safety concern is identified through *AERS*, the Office of Surveillance and Epidemiology (OSE) will conduct epidemiologic studies and communicate this
information to the Center for Drug Evaluation and Research (CDER). Depending on the outcome of the study, CDER can change the product’s labeling, require a risk management strategy, or withdraw the drug from the market.

Under the 2007 FDAAA, the Administration launched *The Sentinel Initiative*. The new system combines claims from existing large, national electronic databases and medical records such as Medicare. This system will allow the FDA to investigate thousands of claims to better characterize an adverse event. The FDA’s goals are to include data from 25 million patients by July of 2010 and 100 million by July of 2012. The claims are far more detailed than reports received through the voluntary system. The FDA envisions a post-approval surveillance system where the *Sentinel Initiative* will compliment the *Adverse Event Reporting System*.

**Communication**

The FDA uses various methods to warn health care professionals and the public when adverse drug reactions arise. As technologies became more advanced and the FDA acquired authority through legislation, new, more sophisticated warning systems were developed. Most recently, the Drugs Safety Oversight Board was established in 2005. This “independent review board,” appointed by the FDA commissioner provides recommendations to the Center for Drug Evaluation and Research regarding the management and communication of drug risks. The committee is currently evaluating its

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11 As done with Trazodone and priapsim  
12 As with isotretinoin and birth defects.  
13 As with Rezulin removed from the market in 2000 due to liver toxicity.
methods of communication and is hoping to alter its policies based on feedback from the community.

Prior to approval, or when questions of drug safety arise, the FDA may require a pharmaceutical company to use a Risk Evaluation and Mitigation Strategy (REMS) in order to ensure a drug’s safe use in the community. REMS is a “strategy to manage a known or potential serious risk associated with a drug or biological product.”(76) The REMS must include a strategy for implementation, subsequent monitoring, and reevaluation.

**Components: Communication with Patients**

According to the Drug Safety Oversight Board, the FDA directly addresses patients through three mechanisms: patient-directed labeling, public health advisories and patient Information Sheets. Patient labeling, otherwise known as medication guides or patient package inserts (PPI), has generated a great deal of controversy. The first PPI was included on the isoproteronol inhaler packaging and warned patients of paradoxical bronchoconstriction with overuse; the safe use of this drug required additional labeling (PPI) in non-technical language to be distributed directly to patients. In 1980, in the wake of the 1979 labeling regulations and numerous studies regarding lack of patient awareness of adverse drug effects, the FDA attempted to include PPI’s with every prescription drug. The proposal met fierce opposition from the pharmaceutical industry due to cost, estimated at $90 million per year. (77) Congress responded to the drug companies by greatly reducing the number of FDA mandated PPI’s to 10 drugs per year. The FDA defines three guidelines under which they require the PPI: Patient labeling will
help prevent serious adverse effects, the drug has serious adverse effects relative to benefits, and patient adherence to directions is crucial to the drug’s effectiveness. (73) Currently, fewer than 30 drugs require patient package inserts.

Public Health Advisories are available through the CDER website and through the Medwatch partners program. They are created to address new safety information, inform the public of the status of an FDA evaluation, and advise of a manufacturer’s suspension of drug marketing due to safety concerns. The drug safety website, launched in 2007, provides links to information on drug labels, medications with Risk Evaluation and Mitigation Strategies, postmarket studies, information from Medwatch, and reviews of drugs undergoing safety evaluations. (78)

In 1998 the FDA began posting information in an easy to understand format and language regarding safe and effective use of all new molecular entities (those that contain an active ingredient not previously marketed in the United States). In 2005, these Patient Information Sheets also included information regarding new safety concerns in an Alert section. (79)

Components: Communication with Healthcare Providers

When the antidepressant and Vioxx cases forced the FDA to reevaluate its drug safety policies, one result was the FDA’s promise to be more transparent in their investigations of safety issues. The FDA now communicates to doctors, nurses and pharmacists through a variety of mechanisms, either directly addressing healthcare professionals in letters, or indirectly through labeling changes.
In 2007 the FDA launched its Drug Safety Newsletter. A similar journal was created in the 1970’s in an effort to communicate completed studies. The Drug Bulletin became electronic in 1984. The journal was renamed the FDA Medical Bulletin in 1991, and discontinued in 1999. The Drug Safety Newsletter’s mission is to “…enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting.”(80) The selected topics are based on safety initiatives identified through the postmarket surveillance system, including ongoing investigations. The Drug Safety Newsletter is emailed quarterly to all subscribers.

The FDA also uses Healthcare Professional Sheets as a mode of direct communication. The sheets serve as a more immediate communication of safety information regarding a drug or drug class. The FDA posts these sheets on the FDA’s website, “Index to Drug-Specific Information”. (81)

Lastly, “Dear Doctor” letters disseminate important information regarding significant hazards to health, announce labeling changes or emphasize corrections to current labeling. They are created by the Pharmaceutical manufacturer. The letter may be issued by the drug company on its own initiative or may be requested by the FDA in response to a drug safety issue. Compliance with recommendations detailed in “Dear Doctor” letters by healthcare professionals, though they contain serious safety information and recommendations, has been dismal. (6, 7)
Other Methods of communication: Risk Evaluation and Mitigation Strategies

The Risk Evaluation and Mitigation Strategies (REMS), formerly known as the Risk Minimization Action Plans (RiskMAP), is a program designed to allow drugs with significant, but manageable risks to remain on the market. Pharmaceutical companies employ three strategies to create a favorable risk/benefit profile: targeted education and outreach, reminder systems, and performance-linked access systems. Targeted education and outreach uses tools such as medication guides, Dear Dr. Letters, FDA alerts and training programs for healthcare providers and patients in an effort to “increase appropriate knowledge and behaviors of key people or groups.” (82) Reminder systems include systems that prompt, remind, and double-check prescriptions in order to minimize risk. Performance-linked access systems include limiting drug administration to a certified healthcare practitioner, and limiting product dispensing only to patients with evidence of a laboratory test (such as required with isotretinoin and the ipledge program). (73)

Labeling: Indirect Communication to Healthcare Providers

The Federal Food, Drugs and Cosmetics Act passed in 1962 included the concept that drugs must be approved for safety, efficacy and for “conditions of use” as specified by the product label. The FDA approves a drug for a specific condition, and instructions for proper use of the drug must be included with the drug in the form of a package insert. Regulations passed in 1979 created the “mandatory” format and content of prescription drug labeling. In 2006, when studies indicated that the labeling had become so lengthy, detailed and complex that healthcare professionals were having difficulty locating
information, the FDA issued specific labeling changes to emphasize important safety information. (3) For instance, the new labels include a section that summarizes key information about indications, risks and dosing at the beginning of the label. (83)

The FDA currently uses three mechanisms to highlight safety information in the package insert: the *Warnings and Precautions* section, typographical warnings, and the Black Box warning. The *Warnings and Precautions* section lists adverse reactions considered clinically significant, and have a serious reaction risk. The order of the list reflects the relative significance of the adverse reaction to public health. In addition, treatment or management strategies for the adverse reaction are discussed. Contact information for reporting suspected adverse drug reactions is listed in the *Adverse Reactions* section. (3)

The typographical warning system, termed by Watson and Barash, is a system of “warning indicators using font and graphical emphasis markings to highlight the most serious and critical information in a label to visually impact the reader.”(3) Use of other fonts, italics, capital lettering, or bolding imparts significance to the information, and the use of a vertical black line in the full prescribing information section indicates recent changes.

**PART III: THE BLACK BOX WARNING**

The black box warning is the highest level of warning issued by the FDA and the most visually prominent information on the package insert. This information is bolded and surrounded on all four sides by a solid black line in an effort to draw the prescriber’s attention to the warning. (3) The warning indicates that the FDA deems the boxed
information to be essential to proper prescription, or aids the physician in monitoring for severe adverse effects.

The 1979 regulation was the first to codify the requirements and the indications for a black box warning. However, the pharmaceutical companies had utilized this tool to emphasize information as early as 1964 in the *Physicians Desk Reference* (PDR). In that year, two drugs included boxed information: Mesulfin (methamine mandelate and sulfamethizole) and Chloromycetin (chloramphenicol). Mesulfin, produced by Ayerst, had a boxed “warning” that suggested doctors inform their patients of benign urine turbidity caused by the drug. (19) The warning persisted on the labeling in the *PDR* until 1974, when Ayerst stopped making the drug.

Chloromycetin (chloramphenicol), called the “wonder drug,” was introduced in 1948 by Parke-Davis. By the 1960’s reports of serious side effects were linked to the use of Chloromycetin. The reports caused a dilemma for the FDA. The drug cured illnesses such as typhoid fever that previously had no effective treatment, but also caused serious blood dyscrasias. In 1951, the listing in the *Physicians Desk Reference* stated that Chloromycetin was “Effective against an impressive array of micro-organisms,” but did not list any adverse effects or warnings. (17) In 1961, Parke-Davis claimed in the *PDR* that, “In patients with certain viral infections, marked clinical improvement, smooth convalescence, and an early return to normal activities may be anticipated. Favorable clinical responses have been reported in patients with viral pneumonia, psittacosis and certain other serious conditions caused by large viruses.”\(^{(18)}\) The labeling, however, now included a warning that chloramphenicol should not be used for minor infections

\(^{14}\) Psittacosis is now known to be caused by a small, intracellular bacterium.
and that “adequate blood studies” should be performed for prolonged or intermittent
therapy. (18)

Despite efforts by the FDA to include warnings in the product labeling,
chloramphenicol was being used “…indiscriminately for such trivial infections as acne
and the common cold.”(84) In response, the FDA issued the first black box warning,
which appeared in the Physician’s Desk Reference in 1964.15(19) The warning stated:

| Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat, or as a prophylactic agent. PRECAUTIONS: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. (19) |

The warning again went unheeded. In 1968 the FDA required the warning on all
of the drug’s labeling and advertising, and “Dear Doctor” letters were sent to every
hospital and physician in the country. (85) The wording of the black box warning was
strengthened and included underlining. The Indications section was bolded and
capitalized, and the Contraindications section reiterated the black box warning and
included underlining. (20)

By 1978, 112 drugs had prominently displayed boxes directly under the name of
the drug in the Physicians Desk Reference, and another 38 had a boxed warning
elsewhere in the labeling (typically under the Warnings section). (21) Though these

15 In 1962-1963, the company only listed the drug’s name in the PDR, and asked the physician to consult the package insert or the company for further information.
boxes were widely used, the FDA had not yet specified the meaning of, and indications for this kind of warning.

**Indications for the Black Box Warning**

The 1979 regulations codified the format and content of prescription drug labeling, including the format and indications for a “prominently displayed box.”(86)

Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. (46)

The regulation also stipulates that the drug manufacturer may not include a black box warning for the drug unless mandated by the FDA. (86)

As stated in the regulation, the FDA indications for a black box warning included problems that may lead to death or serious injury. This broad definition and widespread use of the Black Box Warning lead Dr. Beach and her team to speculate the FDA’s basis for imposing the warnings by surveying 206 black box warnings in 1998. The team determined six criteria to describe the reasons the FDA utilizes the warnings.

(1) early detection of a side effect by physicians may result in intervention that may reverse the adverse reaction;
(2) a well-defined subset of patients are at a higher risk from the treatment;
(3) the risk from the treatment of the particular drug may outweigh the benefits in particular circumstances;
(4) the dosing or drug interaction is pivotal to the risk;
(5) the training of the physician or the setting is crucial; and
(6) there are other special requirements for administering the drug (5)

The FDA did not formally respond to the article, leaving the medical community and the pharmaceutical industry to rely on Beach’s speculations regarding the process, and scientific bases for these warnings.
In 2002 the Associate Director of the Center for Drug Evaluation and Research Policy, Dr. Robert Temple and his colleague Dr. Martin Himmel responded to an article by Lasser, et al. regarding the withdrawal of drugs with black box warnings. (87) They indicated that two side effects, QT prolongation and hepatic toxicity, often the subject of a black box warning, are “now thoroughly examined” in New Drug Applications and adverse event reporting. (88) This was the first indication of what the FDA considered to be high priority when evaluating a drug for approval and subsequently issuing a black box warning.

In 2006 the FDA clarified its stance on labeling by placing a draft Guidance for Industry regarding Warnings and Precautions, Contraindications and Boxed Warnings on the FDA’s website for public comment. It reflects the “current thinking on this topic.” The FDA outlines three situations in which black box warnings are ordinarily used:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g. a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug.
- OR
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g. patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation).
- OR
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted. (89)

The draft guidance also states that the black warning may be used to highlight warning information especially important to the prescriber, or to stress that a particular drug may not be appropriate as first-line therapy. (89) This document outlines the motivation behind an FDA mandate of a black box warning.¹⁶

¹⁶ It is important to note that this guidance is not finalized.
According to Joyce Generali’s Black Box Warning website, there are 505 drugs with a black box warning and 13 with a bolded warning at the beginning of the package insert. (23) Though several drugs with black box warnings have been withdrawn from the market for safety reasons, according to industry experts, no drug has had its black box warning removed. (Personal correspondence with Dr. Bryan Liang and Dr. Louis Morris)

**Impact of a Black Box Warning on Pharmaceutical Companies**

When the FDA issues a black box warning, it becomes very difficult for the drug manufacturer to market the drug. The black box must be added to all drug labeling including brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogues, letters, exhibits, literature, reprints and any other audio or visual materials. (86) In addition, drug manufacturers are prohibited from using reminder advertisements- those that list the name of the drug, company, price and dosage without a discussion of efficacy or side effects.”(90) Broadcast advertisements must include a “major statement,” discussing major side effects and contraindications. (91) For a drug with a black box warning, this entails detailing all the information within the boxed warning. Pharmaceutical companies have used numerous ploys to downplay the message, including distracting music or imagery, and have had to alter their advertisements to comply with FDA standards. Once a drug receives a black box warning, this list of side effects must be included, and poses a serious challenge to delivering a positive message to the consumer.

In addition, many pharmaceutical companies fear litigation once they have admitted previously undisclosed, or under-reported risk. In 2003 the *New York Times*
reported that 9,000 suits had been filed and an additional 32,000 patients may file against Rezulin, a diabetes drug that caused hepatotoxicity and was removed from the market. (92) Redux, an appetite suppressant marketed in 1995, had a known adverse event of pulmonary hypertension when it was approved by the FDA. Within a year, reports of heart-valve damage were linked to the drug as well, leading to its withdrawal from the market. The company has since paid over $20 billion in damages to affected patients. (11) Fear of litigation may also alter doctor’s prescribing habits. A Harris poll in 2003 found that 43% of physicians surveyed have avoided prescribing a particular drug that was appropriate for a patient, because it may be involved in product liability litigation. (93)

The addition of a black box warning may increase negative media attention, especially for high profile drugs like antidepressants. In the years surrounding the antidepressant drug hearings, the New York Times published articles with titles such as, “Study Details Link Drugs and Thoughts of Suicide,” and “Medical Journal Says It Was Again Misled.” (94, 95) An article in 2007, “Psychiatrists, Children, and Drug Industry’s Role,” raised questions regarding experimental treatments in children, reimbursements for doctors, and off-label use of risky drugs. (96)

The combination of marketing difficulty, increased litigation and negative media attention typically leads to a decrease in sales. In the year after Seldane (terfenadine), an antihistamine, received its Black Box warning, sales dropped from $700 million to $450 million. (5) In the years after droperidol, an antiemetic, received its black box warning, there has been a 10-fold decrease in its use in the United States. (97) When Avandia received its black box warning, sales decreased by 60% over a five-month period. (98)
Because of this effect on sales, drug companies often resist altering the package labeling, leading to long “negotiations” between the FDA and the drug companies, and therefore, a delay in informative labeling.

**Impact of a Black Box Warning on Healthcare Professionals**

The purpose of a black box warning is to convey a known risk to healthcare professionals so that they may take appropriate measures to manage that risk. Thomas Scarlett, contributor to *the Food Drug and Cosmetic Law Journal* stated, “Labeling plays a role in medical judgment… Labeling is the most reliable guide for health care professionals using a drug in the daily practice of medicine.”(99) Because the black box warning is meant to convey such ominous side effects, healthcare professionals must take its inclusion seriously.

However, if the black box warning does not accurately reflect scientific studies, doctors may not trust the system to adequately identify serious risk. Beach, et al. noted in their discussion of black box warnings that “It is imperative that the prominence of a warning be proportionate to the risk and supported by data. If the seriousness of the information in the boxed warning is exaggerated, practitioners and pharmacists may become skeptical so that their confidence and reliance on such information will diminish.”(5) In addition, if the FDA fails to respond in a timely manner, doctors may become skeptical of the FDA’s ability to detect adverse reactions and inform the community.
PART IV: PROBLEMS WITH THE BLACK BOX WARNING SYSTEM

The FDA has created the Black Box Warning system to inform healthcare providers and their patients of adverse drug effects. The system is designed to minimize risk, and target the population of patients that would reap the most benefit from the drug. The FDA must balance the necessity to fully investigate an adverse reaction in order to issue the proper response, and the obligation to keep the public informed of serious threats to their health.

Over the past three decades, physicians, epidemiologists, and FDA officials have noted problems with the system. The FDA has been criticized for reacting both too slowly, endangering the lives of more patients, and too quickly, threatening the validity of the warning system. The black box warning has been especially scrutinized because of its importance.

Issues of drug safety over the last thirty years revealed major systemic problems within the FDA regarding the basis on which they detect and investigate adverse drug reactions (generalizability of pre-market data and post-approval surveillance), the rationale for issuing a black box warning (advisory committee-member ties to the pharmaceutical industry), and their ability to effectively communicate this risk to healthcare providers (wording and content of warnings). The FDAAA of 2007 directly addresses many of these issues, which will undoubtedly strengthen the ability of the FDA to detect adverse reactions and provide the FDA Advisory Committees with more complete information. However, the effectiveness of the black box warning system itself depends on the ability of the FDA to reassess previous black box warnings in light of new
data, create consistency when issuing new warnings, and assign new black box warnings only to drugs that deserve the highest FDA warning.

**Generalizability of the clinical trial data**

When the *Kefauver-Harris Amendment* was passed in 1962, pharmaceutical companies suddenly required thousands of patients to participate in clinical trials to prove efficacy. Within a decade of the addition of this requirement, a large pool of patients used extensively in clinical trials was no longer socially acceptable to use in experimentation: prisoners. In 1973, 90% of all pharmaceutical products were tested on prison inmates. (Fig. 7) (100) In the same year Jessica Mitford published an article in the *Atlantic Monthly* entitled, “Experiments Behind Bars: Doctors, Drug Companies and Prisoners.” (101) She accused the drug companies of exploiting a disadvantaged group of people. Drug companies quickly abandoned use of prison inmates as their major source of test subjects due to the negative publicity, well before the FDA published its 1980 policy banning the use of prisoners in clinical trials. (102)

While demand grew and the available population diminished, American citizens were increasingly becoming unusable in clinical trials due to “treatment saturation.” According to Adriana Petryna in her essay on *Globalizing Human Subjects Research*, “our pharmaceuticalized bodies produce too many drug-drug interactions providing less and less capacity to show drug effectiveness and making test results less statistically valid.” (15)

\[17\] Prison inmates promptly sued the FDA, stating this policy violated their right to choose to participate in medical research. The FDA regulations are “indefinitely stayed” regarding this issue, meaning they are in bureaucratic limbo.
Pharmaceutical companies have capitalized on the increasingly global economy by outsourcing the manufacturing of drugs,\textsuperscript{18} and their clinical trials. Contract Research organizations (CRO’s), are companies that facilitate clinical trials by recruiting subjects, monitoring the research, evaluating reports and preparing materials for submission to the FDA.\textsuperscript{19} Some have their own Institutional Review Boards- the people responsible for ensuring the research trial does not expose participants to unnecessary risk or harm. (15) CRO’s received $15 billion from the pharmaceutical industry in 2007, two-thirds of which came from the largest pharmaceutical companies. (104)

The criteria CRO’s use to find patients for their studies include, “local levels of unemployment, population disease profiles, morbidity and mortality rates, per-patient trial costs, and potential for future marketing of the approved drug.” (15) CRO’s often recruit patients from Eastern Europe and Latin America due to collapse of basic healthcare there and because of the widespread absence of treatment for common and uncommon diseases.

CRO’s are expected to continue to grow with the increasing number of phase IV studies, those that examine rare adverse effects and long-term administration of a drug. The use of these populations, in addition to raising ethical questions that are outside the scope of this paper, may complicate the interpretation of how the medication will behave in the U.S. population, a group of individuals taking numerous drugs and with an entirely different nutritional and medical profile. Even within the United States, studies have found statistically significant differences between races in regards to side effects of and response to a drug. (105, 106)

\textsuperscript{18} An action that garnered headlines in the 1990’s when several products from China were contaminated.
\textsuperscript{19} The FDA published a Guidance on this subject, condoning the CRO’s participation in these activities. (107)
In the last ten years, the FDA’s capacity for timely inspection of international manufacturing plants and their ability to prevent harmful contaminants from intentionally or unintentionally entering drugs shipped to the United States has been called into question. (67, 108, 109) The FDA had similar difficulties in investigating clinical trial sites. In 2007, a report released by the Department of Health and Human Services revealed that “federal health officials did not know how many clinical trials were being conducted, audited fewer than 1 percent of the testing sites and, on the rare occasion when inspectors did appear, generally showed up long after the tests had been completed.”(110)

The problems with international clinical trials are most aptly demonstrated through the case of Trovan (trovafloxacin), Pfizer’s antibiotic approved in the United States in 1998. The trial was conducted in Kano, Nigeria, a country suffering from civil unrest under the Abacha dictatorship. Allegedly the investigators did not explain the experimental nature of the treatment, nor did they use informed consent forms (which they later backdated) for the subjects enrolled in the study. They tested the drug in children with bacterial meningitis who were already receiving effective treatment, ceftriaxone, from Doctors Without Borders. They used forms of Trovan that had never been tested in humans, and occasionally gave substandard doses of ceftriaxone, possibly in an effort to create an illusion of superior efficacy of the newer antibiotic.20 This may have resulted in the deaths of eleven children. (13)

Although lawsuits have been unsuccessful thus far, Trovan was withdrawn from the market in 2000 due to liver toxicity. The lack of monitoring, in combination with

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20 Antibiotics are the only class of drugs required by the FDA to be tested against drugs already on the market because a less efficacious drug may pose significant harm, including increased bacterial resistance.
CRO affiliated IRB’s, raises question about the safety of patients and the validity of collected data.

Even when trials are conducted in the United States, certain populations are habitually excluded from participation, raising questions of the relevancy of the trials for the excluded populations. In 2003 a study demonstrated that of 20,388 Medicare beneficiaries hospitalized for heart failure, 75% to 87% met exclusion criteria for three landmark randomized control trials influencing treatment of congestive heart failure. (111) According to Dr. Van Spall, in an article published in the *JAMA*, “Several patient populations, women and children most prominently, have been historically underrepresented in clinical investigations… Similar situations frequently exist for certain ethnic groups, the very elderly, and patients with chronic medical illnesses.”(112)

Dr. Jerry Avorn notes that the situation is particularly acute for the elderly. People over 65 are prescribed over one third of all medications, making them “the most pharmacologically important segment of the society.”(11) The FDA notes that individuals with multiple health problems, particularly older Americans, are at the greatest risk of an adverse drug reaction. (82) Though the elderly are major consumers of medication, and the medicine is likely to react differently in their bodies, they are typically excluded from clinical trials. The FDA has recognized this issue, and encouraged the pharmaceutical companies to include the elderly in their assessments, but has done little to “require” this testing.
The “prescription”: Increased Presence Abroad and Reauthorization of Pediatric Research Equity Act

The current FDA administration has not addressed the growing role of CRO’s since the Guidance published in 2001. Only recently have they focused on globalization of the drug industry. (107) Commissioner von Eschenbach stated, “We have to find our way to station ourselves at the very beginning of the production process, wherever that occurs in the world, and then maintain oversight accountability and responsibility throughout the entire lifecycle of the product... We need to implement initiatives that will enable the agency to be global in its scale.”(113) He plans to accomplish this task by increasing the FDA’s presence abroad. The FDA will disperse personnel in five geographic regions of the world beginning with China, India, and Latin America, and later expanding to the Middle East and Europe. Dr. von Eschenbach believes this will enhance the FDA’s ability to conduct inspections and ensure quality at the outset of production, rather than tracing major disasters once they have reached American soil. This presence may also enhance the FDA’s ability to inspect trials abroad.

The FDA has made several efforts to incentivize or require the testing of drugs in the pediatric population. In 1997, the *Food and Drug Administration Modernization Act* (FDAMA) granted extra months of market exclusivity for drugs tested in children. The incentive was renewed in 2002 under the *Best Pharmaceuticals for Children Act*. Critics claim the incentives have been used by the drug companies to generate an extra six months of profits for blockbuster drugs to treat diseases such as high blood pressure, rather than those typically prescribed to children. (12) In 1997, the FDA passed regulations mandating pediatric testing in certain circumstances. In 2002, the Federal District court ruled that the FDA did not have the authority to require testing. In 2003,
Congress responded by granting the authority through the *Pediatric Research Equity Act*. The legislation allowed the FDA to require drug manufacturers submitting new drug applications to conduct pediatric studies if the drug is likely to be used in a substantial number of pediatric patients. According to pediatric physicians, “more studies [were] conducted in children in the last five years than in the previous 30 years combined.”(114)

Though a great deal of effort has been aimed at encouraging clinical research trials in children, very little has been done to encourage enrollment of other minority populations. The *NIH Revitalization Act* of 1993 mandated participation of women and minorities in National Institute of Health (NIH) sponsored research. However, critics note that 80% of all randomized clinical trials are funded by the pharmaceutical industry, and therefore are not required to enroll these populations. (115) The *FDAAA* of 2007 requires the FDA to formulate “best practices” for enrollment of the elderly, children, racially and ethnically diverse communities and medically underserved populations. In January of 2009, the FDA issued a statement seeking suggestions regarding increased participation of these populations. (115) The FDA did not, however, address the active exclusion of patients over 65 from clinical trials by the pharmaceutical industry. Without legislation creating incentives, or requiring the participation of the elderly, few pharmaceutical companies will seek to include those that may make analysis of trial data more difficult.

**Post-approval surveillance**

The need to monitor a drug’s performance after its approval was recognized in the 1950’s and accentuated with the inception of accelerated drug approvals in the 1990’s.
Prior to 2007, the FDA depended on pharmaceutical companies and healthcare professionals to identify adverse effects and notify the agency. Financial circumstances left the postmarket surveillance division grossly underfunded and understaffed. Moreover, the two systems the FDA use to identify side effects, phase IV clinical trials and the adverse event reporting system, have both garnered criticism for inefficiency, highlighted by recent technological advances, and the inability to generate the informative risk-benefit data necessary for important safety decisions.

**Phase IV Clinical Trials**

Phase IV clinical trials, which follow a large number of patients over an extended period of time, are used as a powerful tool to monitor the safety of medications. These trials identify long term adverse effects, rare adverse affects, and the risks associated with medication usage in a specific population, all of which are difficult to detect in smaller premarket clinical trials. Post-approval commitments are used to investigate safety or efficacy concerns, optimal use of the drug and to ensure consistency and reliability of the manufacturing process. They are typically mandated by the FDA when providing conditional approval of drugs that require further assessment. (116)

Prior to the *FDAAA* in 2007, the FDA could not enforce the completion of the Phase IV clinical trials it previously “required” without taking extreme measures. The FDA could only threaten the company with withdrawal from the market, an action typically reserved for drugs with unmanageable risks. With little incentive to perform the trials, the completion rate for these studies declined from 62% in 1970-1984 to 24% in 1998-2003. (69) In 2002, 820, or 61% of postmarket studies were “pending.”(117) In
2006 899 (71%) were pending, increasing to 911 (71%) in 2007. (116) Of those pending in 2007, 46% were from commitments made before 2003. (116) The information gathered from completed phase IV trials highlights the importance of conducting these kinds of studies in response to suspicious or incomplete premarket data. Forty-one out of 144 completed trials validated concerns regarding safety, efficacy or a drug-drug interaction. Thirty-five of these studies resulted in a labeling change. (116)

**The “prescription”: Penalties and the Reagan-Udall Foundation**

Prior to the Institute of Medicine report, the FDA recognized its inability to effectively manage the completion of “required” clinical trials. In 2006, the FDA commissioned an independent review board to evaluate the development, tracking and review of postmarket commitments. In order to maximize efficiency, the review board recommended limiting postmarket studies to those with specific endpoints, providing better training for all reviewers, and creating a position to review all FDA postmarket trial “requests” to ensure consistency. (116) Also in 2006, the FDA posted a *Guidance for Industry* regarding the proper format and timelines for postmarket clinical trials. (118)

The Institute of Medicine Report directly addressed the FDA’s inability to enforce completion of the “required” trials by recommending monetary penalties for noncompliance. Congress responded to the recommendations by granting the FDA the authority to issue a $250,000 civil penalty for each violation (failure to comply with certain deadlines) and up to $10 million for ongoing violations. (119) The drug manufacturer also must report the status of the clinical trial annually to the FDA, including an explanation of the status. The results of clinical trials are posted on an FDA
website for public viewing. (116) Between March 25 and September 9 of 2008, the FDA issued 21 letters requiring postmarket studies to address safety issues. The FDA is also working with contractors to eliminate the backlog of incomplete commitments.

Though the ability to impose monetary consequence will likely motivate the pharmaceutical industry to complete their postmarket trial requirements, Psaty and Vandenbroucke warn that clinical trials can be designed to avoid answering the FDA’s major concerns. In the case of rosiglitazone, a drug used to treat diabetes, the FDA required post-approval studies to evaluate the drug manufacturer’s claim of a decrease in heart disease resulting from a decrease in diabetes-associated atherosclerosis. The two major postmarket clinical trials, A Diabetes Outcome Progression Trial (ADOPT) and Diabetes Reduction Approaches trial (DREAM), either did not include cardiovascular events as an outcome or underpowered the study for that particular side effect. (120, 121, 122) In 2007, a meta-analysis generated from the drug manufacturer’s own clinical trials that were posted on a public website justified the FDA’s concern regarding the claim. In fact, rosiglitazone users were found to have a 43% higher risk of heart attack or other cardiovascular event. 21 (123) Vigilance in inspecting clinical trial designs will be necessary to ensure the safety concern is being adequately addressed.

In addition to pharmaceutical company-run clinical trials, the creation of the Reagan-Udall Foundation may offer the opportunity to independently investigate drug safety and efficacy. The foundation is a nonprofit research organization created by the FDAAA designed to accelerate innovation, and enhance product safety. The foundation has the ability to investigate the comparative efficacy of what Marcia Angell, former

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21 It is important to note that several studies have not supported Nissen’s findings, which may also highlight the difficulty with using meta-analysis as a basis for issuing a black box warning. (124)
editor-in-chief of the *NEJM*, refers to as the “me too” drugs—those that are structurally similar to others already on the market. (12) Since the FDA only requires a drug to be more effective than placebo in treating a specific disease, drug manufacturers need not prove the drug is more efficacious than those already on the market. Therefore, doctors know little about which cholesterol-lowering drug, atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or one of the combination therapies such as atorvastatin and amlodipine, is the most effective. These types of studies have the potential to provide doctors with vital information regarding which medication is the most effective for a particular disease or patient population.  

**Inefficiencies of Adverse reaction reports**

The *AERS* is a database that combines spontaneous reports from *MedWatch* and mandatory reports from pharmaceutical companies.\(^{23}\) The system has been a major target of criticism since its inception in the 1960’s. Prior to the *FDAAA* in 2007, disorganization and lack of funding left the division of surveillance and epidemiology in the technologic dark ages. In 1997, Murray Lumpkin, deputy director of the FDA’s Center for Drug Evaluation and Research described the agency’s reporting system as consisting of “…200,000 pieces of paper.”(53)

Reporting an adverse event to *MedWatch* entails obtaining the proper forms, collecting a complete past medical history and drug history as well as other pertinent information, and mailing, or emailing the package to the FDA. The process is time-

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\(^{22}\) The landmark ALLHAT study, completed in 2002, compared the efficacy of several groups of antihypertensives. This kind of study is performed very rarely, but has a large impact on daily clinical practice. (105)

\(^{23}\) Please refer to Surveillance and Reporting under Part II: The Warning System for a more detailed explanation of *MedWatch* and mandatory pharmaceutical company reporting.
consuming, and relies on the ability of a healthcare professional to accurately associate a previously unknown side effect with use of a specific drug, which has become increasingly difficult in our “over-pharmaceuticalized” bodies. Because of these issues, researchers estimate that as few as 1% of all adverse events are reported to the FDA.

In addition to sparse reporting, many events that were filed were poorly documented, or incomplete. The inability to properly evaluate cofounding variables creates a difficult situation for the FDA. This is well-illustrated in the case of droperidol, an antiemetic used in post-operative nausea and vomiting, which received a black box warning in 2001 indicating use of the drug may result in fatal arrhythmias (torsades de pointes). Many of the case reports of torsades de pointes associated with droperidol use utilized by the FDA to justify the addition of the black box warning had a cofounding factor. In five of the eleven reports of torsades de pointes, patients had received 600 mg of IV droperidol, 240 times the maximal recommended dose. Only one patient receiving the typical antiemetic dose of 0.625mg experienced torsades de pointes. This patient had cardiovascular complications on admission and had been taking cardiovascular medications, including amiodarone, hydrochlorothiazide and simvastatin. (125) Finally, of the 277 cases reported, several did not include the age or sex of the patient. Both are extremely important in assessing cardiac risk.

An incomplete report may also actually overestimate the number of people affected by a drug. When a serious adverse event occurs, several individuals may submit reports through AERS or to the pharmaceutical manufacturer. If one report is more detailed than the other, or inadvertently contains incorrect information, it may be difficult to determine that two reports are in reality one adverse event. Of the 277 adverse effect
reports concerning droperidol assessed by the FDA, as many as 32 were duplicated reports. (125)

In addition to underestimating or overestimating the number affected, the AERS database does not include the number of people taking the drug, the denominator in determining the percentage affected. If two patients taking a drug acquire irreversible liver damage, the risk is far greater if the total number taking the drug was 10 (20%), as opposed to ten thousand (0.002%).

Finally, the process of further investigating a reported adverse effect may allow dangerous drugs to remain on the market for a long period of time without proper notification to healthcare professionals and the public. Once an adverse effect is identified, it may be entered into the database as a monitored adverse reaction (MAR). In order to qualify as a MAR there must be “a report of a serious, unlabeled, unconfounded, well-documented case with an appropriate temporal relationship between the drug and reaction… or several cases with an appropriate temporal relationship, even with some drug or disease confounding.” (126) Each MAR is evaluated for good documentation, and known reactions in similar drugs. Some adverse reactions warrant the FDA to fund outside investigators to comb through their databases in an attempt to establish a pattern. (127) This system, from the adverse event, to the qualification as a MAR, to the funding of epidemiologic queries by outside investigators, has allowed drugs to remain on the market for years while the adverse event is better characterized. Often, advisory committees must make decisions based on incomplete data due to the inefficiencies of the voluntary reporting system.
The “prescription”: Improvements in AERS and the Sentinel Initiative

In response to the IOM report in 2006, which stressed the post-approval aspect of a drug’s “lifecycle,” the FDA has implemented numerous strategies to increase the effectiveness of the AERS system as well as supplement passive surveillance with active surveillance. The FDA will address the lifecycle issues of a drug by combining all of these tools, modernizing the FDA to incorporate new technologies, and utilizing expert advice from epidemiologists as to how to best analyze and apply this data.

The FDA received a great deal of criticism regarding drugs withdrawn from the market due to safety concerns in the late 1990’s. Many critics blamed this upsurge to hasty drug approvals. The FDA has instituted a pilot program to evaluate new molecular entities at predefined time intervals in order to examine their ability to rapidly and predictably detect problems with newly approved drugs. If this pilot program is successful, the FDA will be applying it to all new molecular entities.

The Critical Path Initiative is an effort to modernize safety assessments using newly developed active surveillance tools. The AERS system will be updated to include improved detection, data mining and analysis tools in order to recognize safety signals earlier, and identify priorities. The FDA is moving towards an all-electronic drug application, and will be cross-linking their databases in order to easily search through the available data. In order to best utilize these new technologies, the FDA has initiated training courses for its medical reviewers in order to conduct better safety assessments.

Additional funding has increased monitoring capabilities by creating 82 positions dedicated to postmarket surveillance.
The FDA has recognized the weaknesses of the AERS system, including the inability to estimate the percentage affected, and has proposed an active surveillance mechanism, the Sentinel Initiative to counteract these issues. The goal of the system is to link private sector and public sector postmarket safety monitoring systems in order to conduct large-scale queries on the incidence of adverse reactions. The FDAAA set the goal of access to data from 25 million patients by July 1, 2010, and 100 million patients by July 1, 2012. (129) The FDA plans to spend $13.5 million on support and strengthening post-market activities in 2009, and gradually increase to $16 million by 2012. (129) The analyses generated by the Sentinel system could estimate the actual risk-benefit ratio, because the denominators (the number of patients using the drug) are known. (4)

Though epidemiologists have generally encouraged the use of large databases to re-evaluate drugs once the drug is released to a larger population, they warn that the information can easily be misinterpreted. Dr. Jerry Avorn notes, “[Confounding by indication] is illustrated several times a year when poorly mentored graduate students discover that patients who take a particular kind of cardiovascular medication are significantly more likely to die of heart failure than patients who didn’t take that medication. Of course they are: their doctor prescribed the drug to treat their heart disease.” (11) Ignoring these pitfalls, and generating data that attracts the press, can lead to thousands of people discontinuing beneficial drugs due to false concerns. In anticipation of these issues, the FDA consulted with industry experts in May 2008 to create a Guidance on epidemiology best practices, which will be made available in 2010. The FDA plans to involve independent epidemiologists to implement these practices and
will involve these experts in decisions regarding important safety concerns. The FDA plans to spend $7.5 million on epidemiology best practices and data acquisition in 2009, increasing to $9.5 million in 2012. (129)

In order to facilitate a unified approach to safety data, CDER established the Quantitative Safety and Pharmacoepidemiology group in 2006. Their goals include developing quantitative methods for safety evaluation, development and dissemination of best practices for reviews of safety aspects of study protocols and providing consistency in review practices and analytical approaches in order to facilitate an exchange of information between the Office of New Drugs and the Office of Surveillance and Epidemiology. This cohesive approach to the “lifecycle” of a drug should create a more comprehensive safety profile.

**Suppression of clinical trial data: Lessons from the Antidepressant Scandal**

In the early 1990’s case reports surfaced of a possible increase in suicidal ideation in adults taking Selective Serotonin Reuptake Inhibitors (SSRI’s), the population for which the drug was approved. An FDA panel voted in 1991 that no hard evidence existed, and the increase could be explained by the illness it was designed to treat. (130) By 1997, off-label use of antidepressants to treat depression in children soared to nearly 600,000 young patients. (131) When Eli Lilly conducted clinical trials on Prozac (fluoxetine) to gain FDA approval for use in children; the study demonstrated only modest improvement in symptoms. (11) Despite a lack of evidence supporting efficacy in young people, physicians continued prescribing the medication to treat child and adolescent depression.
In 2003, when British regulators combined the results of nine Paxil (paroxetine) trials they concluded that paroxetine increased the risk of suicidal ideation in children and banned prescription in young patients. (132) In response to the British drug regulators’ findings, Richard Friedman, a psychiatrist and director of the psychopharmacology clinic at Weill Medical College, stated, “What is disturbing about the recent report is the purported link between Paxil and suicidal thinking comes from an unpublished study sponsored by Paxil’s manufacturer, GlaxoSmithKline. In fact, GlaxoSmithKline has published only one of its nine studies of Paxil in children and adolescents to date.”(133)

The news quickly garnered headlines, and discovery of a cover-up by the pharmaceutical industry generated outrage.

Though mandatory reporting of adverse events is required by law, and their combined clinical trials demonstrated an adverse event, the pharmaceutical industry defended themselves by claiming the individual clinical trials never generated a statistically significant difference. (11) In addition, prior to 2007, clinical trial data were the property of the drug company who conducted the research, and so public release was not required, allowing the pharmaceutical companies to present a skewed version of the data to the public. Reporting only favorable clinical trial data distorts evidence used by physicians when choosing drugs. (134)

In addition to suppressing clinical trial data, the companies manufacturing antidepressants took extra steps to skew the data in their favor. Many pharmaceutical companies outsource their medical writing to agencies, creating drafts of an article and encouraging researchers, a kind of medical celebrity, to endorse the article by signing their name as first author. This practice is referred to as “ghostwriting.” Major journals
such as the *NEJM, JAMA,* and the *British Medical Journal,* peer-reviewed journals that doctors believed to be a source of unbiased data, published several of these articles. In 1999, Pfizer employed ghostwriters to prepare 85 articles on Zoloft (sertraline). By 2001, 55 had been published. (14) In 1999, an article published on Zoloft conspicuously had a section removed that was present in earlier drafts–the section detailing a completed suicide and three suicide attempts in the test group taking the antidepressant. In comparison, none of the patients on placebo attempted suicide. (14) Research performed by David Healy and Dinah Cattell in 2003 revealed that 100% of ghostwritten articles from the company hired by Pfizer were favorable towards Zoloft, whereas only 44% of those written by others reported favorable results. (14)

The antidepressant drug manufacturers were not the only companies suppressing unfavorable data. Bayer is the maker of aprotinin, an antifibrinolytic drug used to reduce perioperative bleeding in patients undergoing cardiac surgery. In 2003 Bayer paid a CRO to conduct a large epidemiologic survey of postoperative complications in patients given aprotinin during surgery. The research demonstrated high mortality rates and renal damage. Disturbingly, “…neither Bayer nor its contractor had provided the report to the FDA or even acknowledged its existence before the [advisory committee] meeting [in 2006].” (14)

**The “prescription”: Logging of clinical trial data**

Congress again responded with a clear message to the pharmaceutical industry through the 2007 *FDAAA.* Drug makers or principal investigators must register clinical trials subject to FDA regulation within three weeks of the first patient beginning therapy.
In addition, clinical trial data must be submitted within 1 year of trial completion or within 30 days of drug approval in order to be posted on a publicly available website.\textsuperscript{24} The FDA may issue fines of $10,000 for failure to submit the data within these deadlines, and may charge $10,000 per day until the trial is submitted if the error is not corrected within 30 days. The clinical trial database will include Internet links to key FDA documents, tables of primary and secondary outcomes, non-promotional summaries, and information on frequent or serious adverse events. (119)

Making these outcomes available will allow researchers outside of the FDA to conduct their own analyses of the data, providing healthcare professionals with unbiased evaluations. It is important to note the limits of the meta-analysis, including the inability to access original data, and thus verify outcomes, as well as a lack of standardized data collecting methods between studies. These deficiencies highlight the importance of well-designed phase IV clinical trials when questions of safety or efficacy arise.

Though the logging of epidemiological studies, such as the study conducted by Bayer regarding aprotinin, is not mandatory, Bayer violated a previous FDA regulation by failing to report a serious, unexpected adverse event within 15 days.

**Committee Ties: Lessons from the Vioxx Scandal**

In 1999, Merck had high hopes for its new drug, Vioxx (rofecoxib), to be a major competitor in the $8 billion a year arthritis ‘painkiller’ market. (136) As early as 2000, the Vioxx GI Outcomes Research (VIGOR) study found that Vioxx users had four times

\textsuperscript{24} Prior to 2007, the public website was available to all pharmaceutical companies that wanted to voluntarily post clinical trial data. This was how Dr. Nissen conducted his meta-analysis that revealed greater cardiovascular morbidity with use of Avandia. Logging of clinical trial data is now mandatory under *FDAAA*. 
as many heart attacks as those taking naproxen. (137) Merck claimed this finding was due to the ability of naproxen to prevent heart attacks, not an increase in risk due to the use of Vioxx. The FDA required Merck to provide this information on its label, but did not require additional research to investigate the finding. (138, 139) In 2001 Vioxx generated $2.6 billion in sales. A trial conducted by Merck to investigate possible use in treatment of colon polyps, which excluded patients with evidence of active coronary disease, was halted early in 2003 when researchers found patients on Vioxx were having twice as many heart attacks and strokes in comparison to placebo. (140) The company voluntarily withdrew the drug in September of 2004.

After weighing all the evidence, an FDA advisory committee surprisingly decided to allow Vioxx and other COX-2 inhibitors back on the market. According to Dr. Jerry Avorn, Chief of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women’s Hospital, “An analysis of the committee’s voting pattern showed that ten of thirty-two panel members had financial ties to the companies that made the drugs being evaluated. Those with such ties were ten times more likely to vote in the drugs’ favor than were members without such ties. Had they recused themselves from the vote, the group would have voted against allowing Vioxx or Bextra to be sold.” (11) Despite the committee’s decision, Merck never brought Vioxx back onto the market.

Expecting advisory committee members to make unbiased decisions regarding drug safety when they have financial ties to the manufacturer is naïve, especially when they must interpret data that is incomplete or inconclusive.

Regardless of financial ties, advisory committees are placed in the difficult position of listening to endless emotional accounts of horrible side effects, as in the child...
suicides associated with antidepressants, and have very few objective tools for evaluating the data. The adverse event reporting system generates sporadic, incomplete data that may under-represent, or over-represent a side effect. Additionally, as mentioned previously in relation to the antidepressant scandal, Dr. Andy Mosholder, an FDA safety evaluator, accused his superiors of withholding data from committees because it was deemed inconclusive. Avorn states, “Obtundation and spasticity are both suboptimal states of arousal. In the absence of an adequate approach to collecting and analyzing data, however, it is understandable that an evidence-deprived agency might resort to either kind of extreme reaction.”(141)

This case demonstrates an under-reaction to a drug’s negative risk-benefit profile by allowing it to remain on the market when other safer drugs were already in use. It certainly calls into question the ability of the FDA to conduct unbiased evaluations of safety information and effectively issue warnings based on available data.

**The “prescription”: Reducing industry ties and creating protocols for committee presentations**

The results from the Vioxx advisory committee meeting motivated the FDA and Congress to address industry ties. In March of 2008, the FDA issued a guidance imposing strict criteria regarding committee participant waivers. The FDA is focusing on public disclosure and increasing epidemiology expertise in advisory committee meetings. The mission of the guidance is to “…increase the transparency, clarity, and consistency of the advisory committee process and enhance public trust in this important
function.” (142) The FDAAA requires a reduction to 95% of 2007 waivers by 2008; and a reduction to 75% of 2007 waivers by 2012.” (119)

The FDA has recently created standard operating procedures, defining what kind of information will be made available to the public from committee meetings, and how the FDA will present information to the drug safety advisory committees. (89) This directly addresses the issues raised by the Vioxx scandal and allegations that the FDA favored industry interests by withholding specific data from safety advisory committees.

Issues of Communication

Part I: Lessons from Troglitazone and Dear Dr. Letters

Over the last 100 years, the FDA has focused a great deal of time and energy on communicating the true contents, benefits and risks of drugs to healthcare practitioners and their patients so that they can make informed decisions. The labeling system has been altered in order to stress the most important information, and impart a sense of urgency when a drug has serious associated risks. The agency’s authority over labeling information has increased greatly since the 1906 Pure Food and Drugs Act. However, prior to the 2007 legislation, the FDA had to negotiate the content and wording of all labels with the pharmaceutical company. The inability to reach an agreement led to long delays in the communication of critical information.  

The black box warning is meant to communicate risks that are so clinically significant that the use of the drug may result in permanent impairment or death. The warnings are essential if the risks can be avoided through selective prescription of the

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25 It took 14 months to negotiate the labeling changes for Vioxx to reflect its detrimental effects on the cardiovascular system. (143)
drug to the proper patient, careful monitoring, or avoiding concomitant use of other
drugs. Unfortunately, numerous studies investigating the healthcare practitioner’s
compliance with these warnings has found their response to be dismal. In 2001 Dr David
J Graham, the associate director at the Office of Post-approval Drug Risk, published an
article investigating the consistency of FDA recommended liver enzyme testing with the
use of troglitazone, a drug known to cause acute liver failure. The FDA issued four Dear
Healthcare Professional letters and a labeling change over its lifecycle in an effort to
promote proper use of the drug. The study found that the warning had some immediate
initial effect, but by 3 months, less than 5% of patients received all of the recommended
testing. (7)

In 1992, Weatherby and her colleagues specifically investigated the use of certain
language and doctors’ prescribing habits in response to these letters. They found that
concise, focused wording of the warnings resulted in the highest compliance. When the
FDA or drug companies did not specifically indicate which drugs were contraindicated,
and instead used language like “certain members of classes were said to be
contraindicated,” the response was weaker. (6)

Two studies published in 2006 investigating the use of medications with a black
box warning concluded that practitioners either had difficulty following the warnings, or
that they were unaware they existed. The study by Wagner, et al discovered that black
box warnings recommending laboratory testing were the most widely disregarded
(49.6%), whereas practitioners adhered to those focused on risks in pregnancy (.3%).
(144) Though the study by Lasser and her colleagues reported a much lower rate of
nonadherence to the warnings, they found that more than half of the black box warnings required clarification from specialists. (145)

The regulations passed in 2006 requiring all new drugs to adhere to a specific labeling format did not address the current wording of the black box warnings. Though the ability to find the information is imperative, the aforementioned studies demonstrate the importance of brevity and clarity when communicating these risks. Though the draft guidance from 2006 states that a warning should contain a “…brief, concise summary of the information that is critical for the prescriber to be aware of,” many of the black box warnings are comprised of multiple sentences consisting of language that may not be clear to all practitioners. (89) For example, the black box warning for metoprolol, a commonly used beta-blocker contains 118 words, and restates the same point several times.

**Ischemic Heart Disease:**
Following abrupt cessation of therapy with certain beta-blocking agents, exacerbation of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina develops, TOPROL-XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician’s advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TOPROL-XL therapy abruptly even in patients treated only for hypertension. (22)

In addition, there is no official FDA list of all drugs with a black box warning, nor can one find the black box warning for a drug like chloramphenicol on its website, a drug with a forty year history of containing the warning.
Part II: Lessons from Naproxen and Droperidol

Complex wording and difficulty finding adequate information may be major reasons that doctors do not comply with the black box warnings. However, a third, more important reason may be at the heart of non-adherence: a lack of trust in the FDA’s judgment. As mentioned previously, Beach and her colleagues noted that an exaggeration of risk only serves to weaken the strength of the warning. Practitioners have questioned the reasoning behind the black boxes issued for drugs such as naproxen, carbamazepine, and droperidol, all drugs that may have unfairly received the agency’s highest warning.

In 2005, after a great deal of negative publicity surrounding the Vioxx scandal, the FDA chose to add a class Black Box warning to all coxibs and non-selective non-steroidal anti-inflammatory (NSAID) agents due to increased cardiovascular risk and gastrointestinal adverse effects. Naproxen, a non-selective NSAID was among the drugs that received a black box warning. It stated,

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS). These NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary bypass graft (CABG) surgery. (22)

This was the same drug that Pfizer claimed had such strong cardioprotective affects, it was unfairly skewing the data in the 2000 VIGOR study that demonstrated the negative

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26 Naproxen acquired its black box warning through an NSAID class warning, despite its cardioprotective effects.
27 Carbamazepine also received a class black box warning for all anticonvulsants even though its odds ratio for suicidality demonstrated a decrease, not an increase in suicides.
28 Droperidol was a commonly used postoperative antiemetic. It received a black box warning in 2001 indicating it prolonged the QT interval, which may result in a fatal arrhythmia. Subsequent studies have shown that when the recommended doses are used, no cause and effect relationship can be established.
cardiovascular effects of Vioxx, an argument accepted by the FDA. Additional studies have found naproxen to have a mild cardioprotective affect. (146)

In addition to issuing black box warnings that may not be warranted, the FDA has not established a consistent approach to addressing potential dangers. In 2001, the FDA issued a black box warning for droperidol based on case reports demonstrating a positive dose-response relationship with QT prolongation. The act of issuing a black box warning shifted the treatment of post-operative nausea and vomiting from droperidol to the 5-HT3 antagonists (i.e. ondansetron). Further studies demonstrated that the 5-HT3 antagonists also cause QT prolongation. (147) However, no black box warning has been issued for this class of drugs.29

The FDA reacts rapidly when issuing or strengthening a warning. However, evidence that a black box warning needs to be clarified, or removed, often goes unaddressed. Several drugs have been withdrawn from the market in years after a black box warning has been issued and black box warnings have been strengthened, however, no black box warning has been downgraded. (135, 145) Overreaction, and the issuing of unwarranted warnings have resulted in growing distrust of the warning system.

The “prescription”: More authority and review committees

The FDA has acknowledged a disconnect in their ability to effectively communicate risk to healthcare providers and the public. In 2005, they developed the Drug Safety Oversight Board in order to manage important safety issues including

29 In 2003, the FDA reconvened an advisory committee to address the black box warning issued for droperidol in 2001. Despite expert testimony from cardiologists questioning the validity of using the QTc interval as a surrogate marker for torsades de pointes, and the lack of data gathered by the FDA since 2001, the FDA did not change the black box warning. 5-HT3 antagonists were not addressed. (149)
assessing the need for FDA-approved patient labeling, and overseeing development and implementation of drug safety policies. (147) The Board published a guidance addressing how the FDA communicates with healthcare providers and patients, and vowed to reevaluate based on public responses. The FDA will also utilize user fees to sponsor independent research to determine the best way to maximize public health benefits in reporting serious and nonserious adverse events. (150)

The FDA is evaluating its systems to prevent improper use of dangerous drugs. They plan to issue a draft Guidance regarding “Dear Doctor” letters in the near future. This document may address the need for direct, concise language when communicating serious risks to doctors. The FDA has also required evaluations of the Risk Evaluation and Mitigation Strategy systems at 18 months, 3 years and again at 7 years. (119) Additionally, the FDA will evaluate the overall effectiveness of one or two of these systems annually, with open comment from experts and the public. In order to keep the public adequately informed, the FDA will consolidate the list of approved REMS onto a publicly available website. Finally, the FDA has plans to issue guidances for the pharmaceutical industry regarding hepatotoxicity and cardiovascular risk, the two major adverse effects that Temple identified as those that are “thoroughly investigated” in his article in JAMA in 2002. (88)

The 2007 FDAAA granted the FDA the authority to require labeling changes or REMS, and the ability to enforce these requirements. If the FDA and the pharmaceutical company have not agreed upon a labeling change through negotiations within 30 days, the FDA can simply mandate the change. The fiduciary penalties for noncompliance with labeling changes or REMS are $250,000 for each violation, and up to $10 million
for ongoing violations. (119) Since March 25, 2008, the FDA has required five labeling changes: a boxed warning for conventional antipsychotics, a boxed warning for fluoroquinolones, a boxed warning for oral phosphate products (bowel preps), strengthening boxed warnings for erythropoiesis-stimulating agents, and strengthening of the boxed warning for tumor necrosis factor. Critics claim the agency is requiring these changes even when there is not sufficient evidence of a causal association. (135) This newfound labeling authority may serve to further undermine the effectiveness of the warning system if the data do not support the need for the highest level of caution.

The FDA reconvenes drug safety advisory committees when an issue arises, such as in the case of the droperidol black box warning. Under the 2007 FDAAA, the FDA must readdress the efficacy and application of REMS protocols. In order for the black box warning system to be effective, the FDA must similarly re-evaluate black box warnings at set intervals to evaluate the necessity and the effectiveness of that warning, as well as new data.

**Conclusions:**

The FDA has undergone a major ideological shift in their approach to drug safety over the last 100 years, and has recently been granted the resources and authority to implement new solutions through cutting-edge technology. The Administration has come a very long way from the “Poison Squads” of the early 1900’s. After decades of increasing authority and reputation, budget cuts, staff turnover and disorganization recently have caused the public to distrust the agency’s ability to adequately protect them from dangerous drugs.
Prior to the 2007 FDAAA, physicians and epidemiologists criticized the drug evaluation system for requiring “the FDA, clinicians, patients and payers to make decisions about drug use in data-poor environment.”(151) Decisions made by committee members reflected this lack of information by both under-reacting and overreacting to safety signals. Healthcare providers became disenchanted with a system that appeared to be heavily influenced by the pharmaceutical industry. This attitude was conveyed through numerous articles rejecting the FDA’s decisions regarding black box warnings and health care professionals’ subsequent dismal response to recommendations conveyed through Dear Doctor letters and labeling changes.

The FDA is in the difficult position of needing to fully assess adverse event reports in order to issue informative, accurate warnings, so as not to unduly raise alarms, and the need to keep the public fully informed of risks to their health. The FDA has gracefully accepted criticism and constructive suggestions from outside sources in order to improve their systems. In their Response to the Institute of Medicine, FDA officials stated, “FDA has begun to take the steps required to: (1) further scientific understanding of drug products’ benefits and risks, (2) rely on this understanding for regulatory decisions about drug marketing, and (3) communicate this understanding to healthcare professionals, patients, and the public so that they can make prescribing decisions based on the best scientific information available.”(150)

The FDA has the opportunity to revolutionize the way they approach safety information, and may be able to fully inform their committees before they make important decisions about a drug’s risk-benefit profile. In addition to restructuring the basis of the warning system, the FDA must re-evaluate decisions made in a previous,
data-poor environment, and issue the black box warnings only to those drugs that truly
deserve the agency’s highest warning. New authority to issue labeling changes should
not be interpreted as complete freedom to act without proper supporting data. By
removing the inappropriate uses of black box warnings, the FDA can restore clout to the
warning system, and may reestablish their relationship with healthcare professionals.
The FDA must also centralize the information, and simplify the wording of the warnings
in order to allow doctors to be able to quickly locate the brief, concise communication of
serious risk.

As drugs become more advanced, and risk-benefit profiles more complex, the
FDA will face new dilemmas regarding drug safety. A warning from the FDA has a
dramatic effect on how the public perceives a drug, and therefore how physicians utilize a
drug. The consequences of issuing a black box warning must be weighed against the
importance of full disclosure. The enormity of the responsibilities entrusted to the FDA
has been grossly underappreciated and underfunded over the last 50 years. The FDA’s
ability to utilize resources and authority granted by the 2007 Food and Drug Amendments
Act has the capability to reestablish its place as a leader in innovative scientific
approaches to drug evaluation and safety.

30 In the case of antidepressants, the consequence may be a decrease in diagnosed and/or treated
depression, leading to an increase in completed suicides. In the case of droperidol, the consequence was
increased use of a more expensive, equally risky anti-emetic- a significant consideration in a time when
medical expenses have been increasing exponentially.
Figures

Figure 1: “Founding of the United States Pharmacopeia, 1820.” http://www.usp.org/aboutUSP/history.html
Figure 2: Mrs. Winslow’s Soothing Syrup Ad from the late 1800’s. Courtesy of the FDA Office of History.
Figure 3: The “Poison Squad” of 1906. Dr. Harvey Wiley, Commissioner of the Food and Drug administration, is third from the left in the back row. Courtesy of FDA Office of History.
Figure 4: Dinitrophenol compounds from the 1930’s. Courtesy of the FDA Office of History.
Figure 5: Press release from the FDA regarding the dangers of Dinitrophenol. Courtesy of the FDA Office of History.
Figure 6: Senator Kefauver (left) at a Congressional Hearing. Courtesy of the FDA Office of History
Figure 7: Prison inmate testing in Holmsburg Prison, Philadelphia, PA.
APPENDIX: ABBREVIATIONS

ADOPT ........................................................................................................... A Diabetes Outcome Progression Trial
AERS .................................................................................................................. Adverse Event Reporting System
AMA .................................................................................................................. American Medical Association
CDER .................................................................................................................. Center for Drug Evaluation and Research
DDMAC .............................................................................................................. Division of Drug Marketing Advertising Communication
DESI ...................................................................................................................... Drug Efficacy Study Implementation
DREAM .............................................................................................................. Diabetes Reduction Approaches Trial
DTC ...................................................................................................................... Direct to Consumer
FDA .................................................................................................................... Food and Drug Administration
FDAAA ............................................................................................................. Food and Drug Administration Amendments Act
FDAMA ............................................................................................................. Food and Drug Administration Modernization Act
HIV ...................................................................................................................... Human Immunodeficiency Virus
IOM ...................................................................................................................... Institute of Medicine
JAMA .................................................................................................................. Journal of American Medical Association
MAR .................................................................................................................... Monitored Adverse Report
NEJM .................................................................................................................. New England Journal of Medicine
OND .................................................................................................................... Office of New Drugs
OSE .................................................................................................................... Office of Surveillance and Epidemiology
OTC .................................................................................................................... Over the Counter
PDR ..................................................................................................................... Physicians’ Desk Reference
PDUFA ................................................................................................................ Prescription Drug User Fee Act
PPI ......................................................................................................................... Patient Package Insert
REMS .................................................................................................................. Risk Evaluation and Mitigation Strategies
SSRI ..................................................................................................................... Selective Serotonin Reuptake Inhibitor
USP ..................................................................................................................... United States Pharmacopoeia
VIGOR ................................................................................................................. Vioxx GI Outcomes Research
References


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