# The Hidden Lesson of the Vioxx Fiasco: Reviving a Hollow FDA

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## Executive Summary

On September 30, 2004, Merck & Co. Inc. announced that it was voluntarily withdrawing its blockbuster pain medication, Vioxx. By then, 20 million people had taken the drug, resulting in annual sales of $2.5 billion. Merck's decision came after interim results of a clinical trial it had commissioned showed that long-term use of Vioxx was associated with a nearly doubled risk of heart attack or stroke. Later, testifying before the Senate Finance Committee, Dr. David Graham, Associate Director for Science and Medicine in the Food and Drug Administration's (FDA) Office of Drug Safety estimated that between 88,000 and 139,000 Americans suffered a heart attack or stroke as the result of taking Vioxx. He warned, "FDA, as currently configured is incapable of protecting Americans against another Vioxx. We are virtually defenseless."

What happened? Pundits provide multiple theories. Some focus on Merck's conduct. After one of its own studies showed a large increase in the risk of heart attacks among patients taking Vioxx as compared to patients taking naproxen, the company tried to explain away the apparent risk and urged its sales staff to avoid talking about the study with doctors. Instead of encouraging frank discussion about the data, Merck urged its sales staff to rely on a "Cardiovascular Card," which contained information from older, smaller studies and suggested Vioxx might actually protect against heart attacks. Such conduct has prompted the filing of thousands of personal injury lawsuits, the first of which resulted in a $253 million verdict against Merck. The company has vowed to appeal that case, and to defend each claim, one by one.

Another suggestion as to the reasons for the Vioxx catastrophe is that the culture within FDA has become too closely aligned with the interests of the pharmaceutical industry the agency is charged with regulating. Other critics charge that FDA is rushing new drugs onto the market too soon.

Rarely mentioned is the possibility that FDA has become another "hollow" government agency, so short of funding that it cannot do what Congress – and the public – rely on it to do. Shortfalls in funding, combined with failures in political will and companies left free to take excessive risks to beat their competitors onto the market, have produced a "defenseless" agency, to use the term applied by one of its senior officials, Dr. David Graham, in congressional testimony delivered soon after the Vioxx scandal broke. This report focuses on the reasons behind the imbalance between funding of FDA's pre-market and post-market functions, and the resulting inability of FDA to effectively monitor the safety of drugs after they are on the market.

As its history demonstrates, the FDA is a critical public agency, necessary for ensuring the safety of the nation's food and drug supply. Conservative economic theorists and interests within the pharmaceutical industry, however, have argued that since FDA averted the thalidomide tragedy in the 1960s by requesting additional information on the drug and stalling its entrance onto the U.S. market, the incentives within the agency with respect to prescription drugs have been out of alignment, leading to overly protective decisionsmaking by drug reviewers and unreasonable delays in getting new drugs to market. In the 1980s, advocates joined in the call for more speedy approvals for drugs critical in the fight against the emerging AIDS epidemic. The Prescription Drug User Fee Act of 1992 (PDUFA) was intended to improve the speed with which FDA approved new drugs and ameliorate the so-called "drug lag" problem.

The focus on speeding up the drug approval function of the FDA separates out one piece of FDA's critical function as the insurer of drug safety but fails to bring along the counterpart, equally essential function – monitoring drugs once they are on the market. Vioxx is the latest reminder that FDA cannot foresee all safety risks before it approves a new drug; indeed, serious side effects sometimes emerge only after drugs are approved and taken by large numbers of patients under real world conditions.

### *Inadequate Post-approval Monitoring*

As it was intended, PDUFA sped up new drug approvals. It also caused a severe imbalance in resources at FDA, to the detriment of post-market drug safety activities. The pharmaceutical industry's goal in agreeing to pay user fees was to help speed up FDA's review of new drug applications, and thus get new drugs approved and to market sooner. This goal would only be met if fees were restricted for use on new drug review activities, and did not merely substitute for, but added to, appropriated funds for new drug reviews. Therefore, the law that authorized FDA's collection and use of industry fees specified that they could only be used: 1.) for new drug review activities; and 2.) provided that FDA continued to allocate the same amount of congressionally appropriated funds to new drug review as the year the law was passed.

These restrictions, combined with lagging congressional appropriations, meant that in the years that followed, FDA was forced to cut appropriated funds from other uses in order to keep its budget of appropriated funds for new drug reviews high enough to be able to spend the user fees. Activities that supported post-market drug safety monitoring were among those sacrificed to keep enough money flowing into new drug reviews. Specifically, in 1992, the year the law was passed, FDA's Center for Drug Evaluation and Research spent about 53 percent of its budget on new drug reviews. By 2002, the amount of CDER's budget devoted to reviewing new drug applications had increased by nearly half – to 74 percent. In that same year the Office of Drug Safety, which is part of CDER and responsible for monitoring the safety of drugs once they are on the market, comprised only six percent of CDER's budget.

The result of the imbalance between FDA's pre- and post-market safety reviews is that the agency, and thus the public, has become increasingly reliant on industry to detect safety risks that emerge only after a drug is on the market. That arrangement raises concerns for several reasons. As of 2005, FDA reported that of the nearly 1,200 post-market safety studies that drug companies committed to perform, nearly 70 percent have not yet begun. Moreover, companies' financial stakes in the continued sale of approved drugs pose a serious conflict of interest in decisions of whether and when to withdraw products that prove dangerous once on the market.

Only FDA can objectively ensure that the public benefits from faster access to new drugs continue to outweigh the risks posed by those drugs. Congress made technical adjustments to the user fee law in 2002 to help cure the funding imbalance between FDA's pre- and post-market review functions, but performance goals related to new drug review remain, and amounts planned for risk management programs represent a small fraction of overall funding. To truly bring balance to FDA's drug safety reviews, Congress must infuse the agency with appropriated funds sufficient to allow FDA to allocate sustained resource increases to its Office of Drug Safety.

In addition, Congress should: 1.) eliminate new drug review performance goals so that FDA can translate into action its newfound ability to allocate user fees to post-market drug safety; 2.) authorize FDA to impose substantial civil monetary penalties on companies that fail to follow through on commitments to conduct post-market safety studies; 3.) authorize FDA to demand, not negotiate, revised product labeling when new safety risks emerge after a drug is on the market; and 4.) provide FDA with the funds and the mandate to evaluate whether warnings concerning drug safety risks are achieving their intended effect.

## *'The Single Greatest Drug Safety Catastrophe' in U.S. History*

The FDA approved Vioxx in May 1999 as a prescription painkiller for use, among other things, as a treatment for the signs and symptoms of arthritis.[1] Vioxx was one of the "COX-2 inhibitors," a class of drugs that also includes Pfizer's Celebrex and Bextra.[2] None of the COX-2 drugs were ever shown to provide more effective pain relief than many older, less expensive non-steroidal anti-

inflammatory drugs (NSAIDs) including ibuprofen, aspirin and naproxen.[3] However, FDA granted Merck a six-month priority review for Vioxx because it promised an advantage over existing NSAIDs: fewer gastrointestinal (GI) side effects, including bleeding.[4]

The COX-2 inhibitors and older NSAIDs fight pain by blocking enzymes in the body called cyclooxygenase (COX), which contribute to pain and inflammation.[5] The role of the two forms of COX enzymes in the body is not fully understood.[6] What is known is that the COX-1 enzyme is needed for normal functioning of the stomach and of platelets.[7] COX-2 is thought to be responsible for the pain and swelling associated with conditions such as arthritis.[8] Traditional NSAIDs block both COX-1 and COX-2, and thus, in addition to relieving pain, increase the risk of stomach bleeding, ulcers and other GI complications.[9]

The COX-2 inhibitors, on the other hand, target and block COX-2 more than COX-1.[10] Evidence suggests that COX-1 helps promote blood clotting, while COX-2 helps retard it.[11] Under normal conditions, the forces that promote clotting and the forces that prevent it work in a delicate balance to maintain blood flow through the body, but prevent blood loss from injuries.[12] While blocking COX-2 but not COX-1 may fight pain and inflammation without causing GI upset, it may also promote excessive blood clotting.[13] Excessive clotting, in turn, can lead to heart attacks or strokes. When a blood clot forms (often at the site of an injury) in a vessel that brings oxygen and nutrients to the heart or brain, it can stop blood flow through the vessel, which causes a part of the heart or brain to be injured or die.[14]

Increased risk of heart attacks and other cardiovascular events, including strokes, was precisely the reason for Merck's voluntary withdrawal of Vioxx from the market in 2004.[15] Merck's decision came after results from its large, randomized placebo-controlled clinical trial designed to evaluate the effectiveness of Vioxx in preventing recurrence of colorectal polyps (APPROVe) showed that, beginning after 18 months of treatment, 3.5 percent of patients taking Vioxx suffered heart attacks or strokes – nearly double the 1.9 percent taking a placebo.[16]

### *What Did Merck Know, and When?*

Critics charge that Merck – badly in need of a new drug to replace revenues lost when patents on several of its popular drugs expired in 2000 and 2001 – knew about the significant cardiac risks of Vioxx years before its voluntary withdrawal.[17] Indeed, indicators of cardiac risk were present before FDA ever approved Vioxx for market. Merck's small, short-term, pre-market studies were "adequate to evaluate relief from pain as well as some of the more common adverse effects such as high blood pressure, fluid retention, and abnormal laboratory tests for kidney function," but were "not adequate to evaluate the health effects of Vioxx on less common but important health outcomes such as heart attack and stroke."[18]

Even those studies, however, indicated some cause for concern – 0.74 percent of patients taking Vioxx experienced a cardiovascular event, as compared to 0.24 percent taking a placebo.[19] Combined with the known effects of COX-2 inhibitors on clotting, the difference observed provided cause for concern sufficient to prompt an FDA reviewer to warn that while available data did not provide a basis to say with complete certainty whether Vioxx increased the risk of heart attack and stroke, "[a] larger database will be needed to answer this and other safety comparison questions."[20]

In January 1999, just months before Vioxx was approved in May of that year, Merck began a randomized clinical trial called VIGOR, intended to evaluate the effects of Vioxx on major upper-GI events such as bleeding, perforation and obstruction.[21] The trial included patients 40 years and older with rheumatoid arthritis, and was designed to compare health outcomes experienced by patients taking Vioxx against those of patients taking naproxen.[22] The results of the Vigor trial indicated that in 1000 patients followed for a year, Vioxx treatment would likely be associated with 24 fewer GI events (only about eight of them complicated or severe) and 6 more heart attacks than naproxen treatment.[23]

FDA stresses the fact that, "it is important to understand that all approved drugs pose some level of risk, such as the risks that are identified in clinical trials and listed on the labeling of the product."[24] FDA will not approve a drug unless its "demonstrated benefit outweighs its known risk for an intended population."[25] The VIGOR

trial, which was large enough to exclude chance as a credible explanation for the differences in rates of GI and cardiovascular events, presented a difficult risk-benefit choice.[26] Drug safety expert Dr. Bruce Psaty, testifying before the Senate Finance Committee, described the trade-off as follows:

> On the one hand, GI events are more common than cardiovascular events in the population included in VIGOR; although they are potentially serious, they are not usually fatal, and recovery is generally complete. On the other hand, about 25 % of heart attacks are fatal. For persons who survive an initial heart attack or stroke, the quality of life and the duration of survival are usually compromised.

FDA did not have the results of the VIGOR trial to consider prior to approval, however – the VIGOR results were only available in December 1999, seven months after Vioxx was approved. Had the results of the VIGOR trial been available earlier, FDA may have postponed approval of Vioxx pending additional studies.[27]

As it was, Vioxx was already on the market. Merck chose to interpret the increased incidence of cardiovascular events in patients taking Vioxx in the VIGOR trial to mean not that Vioxx *increased* the risk of heart attack and stroke, but that naproxen's aspirin-like effect *decreased* the risk of heart attack and stroke.[28] The five-fold difference in the risk of heart attacks shown by the VIGOR trial, however, is too large to be explained by the protective effects of naproxen – as measured against Merck's own 1996 hypothesis on the size aspirin's beneficial effects (25-30 percent) and observational studies on naproxen's (15-20 percent).[29]

Merck's chosen theory of the VIGOR results prompted FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) to issue a warning letter, charging that the company's statements were "false, lacking in fair balance, or otherwise misleading."[30] Specifically, FDA rebuked Merck for failing to disclose that its theory of the results was "hypothetical, [had] not been demonstrated by substantial evidence, and that there is another reasonable explanation" – that Vioxx may increase the risk of heart attacks and strokes.[31] FDA did not, however, ask that Vioxx be withdrawn on the basis of the VIGOR results, nor did it request the strongest "black-box" warning to be added to Vioxx's label.[32] Instead, FDA requested that Merck include the information in the "warnings" section of the product label.[33]

But FDA does not write prescription drug labels – rather, the agency must negotiate, and reach agreement, with the drug's manufacturer.[34] The Vioxx label was not changed to address the cardiovascular risks indicated in the VIGOR trial until April 2002 – more than two years after the results of the Vioxx trial were made public, and more than one year after FDA's public review of the VIGOR results.[35] Although part of the delay was attributable to FDA's need to convene an advisory committee and conduct analyses, approximately six months were eaten up by Merck's resistance to a variety of label changes proposed by FDA.[36] The agency wanted Merck to add language about the VIGOR results and cardiovascular risks in the "warnings" section of the label.[37] Merck wanted the information to appear in the less urgent "precautions" section – a result that the company's former head research scientist privately expressed he would consider "a miracle."[38] Ultimately, FDA relented and Merck revised the label's "precautions" section.[39] Testifying in court, Merck executive David W. Anstice recently provided the explanation for the company's negotiation stance: it forecast a $500 million drop in sales if the information appeared in the "warnings" section instead.[40]

Meanwhile, Merck's $100 million per year direct-to-consumer marketing campaign[41] contributed to the use of Vioxx by 20 million patients.[42] Only a minority of the patients using Vioxx actually required the GI benefit promised by Vioxx but lacking in older, cheaper NSAIDs, which were equally effective at relieving pain.[43] Following the results of the VIGOR trial, to ensure continued high levels of Vioxx prescriptions (and thus sales), Merck directed its sales staff to avoid discussing the VIGOR results with doctors.[44] Instead, the company urged adherence to a "new resource" – a pamphlet called the "Cardiovascular Card."[45] Based on data from short-term pre-market trials of Vioxx, the Cardiovascular Card claimed that patients taking Vioxx were 11 times less likely to die than patients taking other NSAIDs and had a 50-percent less chance of having a heart attack than patients taking a placebo.[46]

While increasing risk by maximizing patient exposure, another effect of the high level of Vioxx use driven by Merck's marketing campaign was to permit various investigators, including FDA's Dr. David Graham, to conduct observational studies of the association between Vioxx and the risk of heart attack.[47] In observational, or epidemiologic studies, "investigators examine the associations between risk factors and health outcomes that occur naturally in the community."[48] Dr. Graham had become concerned about the potential public health risk posed by Vioxx as the result of the VIGOR study.[49] Working with colleagues and with Kaiser Permanente in California, Dr. Graham used computer records maintained by that health maintenance organization to compare the incidence of cardiovascular events in patients using Vioxx against those using Celebrex, Pfizer's COX-2 inhibitor.[50] The study, which took nearly three years to complete, concluded that Vioxx was associated with a 50 percent increase in the risk of heart attack when taken at doses of 25 milligrams (mg) or less per day, and a 370 percent increase when taken at doses greater than 25 mg per day.[51]

Dr. Graham presented the results of his study in August 2004 to senior management within FDA.[52] He and his colleagues had planned to present their conclusions – that high-dose Vioxx significantly increased the risk of heart attacks and sudden death and should not be prescribed to or used by patients – at the International Conference on Pharmacoepidemiology in Bordeaux, France later that month.[53] Instead, according to Dr. Graham, he was pressured to change his conclusions and "basically threatened that if [he] did not change them, [he] would not be permitted to present the paper at the conference."[54] According to FDA, Dr. Graham voluntarily chose to revise the conclusions after some FDA scientists questioned his conclusions – particularly the recommendation of never using high dose Vioxx.[55]

The next month, Merck was confronted with interim results of its own APPROVe study, indicating that beginning after 18 months of treatment, the risk of heart attack or stroke doubled for patients taking Vioxx as compared to a placebo.[56] On the basis of these data, the independent Data Safety Monitoring Board for the APPROVe trial recommended that the study be stopped early for safety reasons.[57] On September 30, 2004, after tens of millions of people had taken the drug, and annual sales had reached $2.5 billion,[58] Merck withdrew Vioxx from the market.[59]

*FDA's Dr. David Graham estimates that between 88,000 and 139,000 Americans experienced heart attack or stroke due to Vioxx, 30-40 percent of which likely resulted in death. He has characterized the public health impacts of Vioxx as perhaps 'the single greatest drug safety catastrophe in the history of this country or the history of the world.'*

Dr. Graham estimates – based not on his own study, but on the risk levels demonstrated in Merck's VIGOR and APPROVe trials – that between 88,000 and 139,000 Americans experienced heart attack or stroke due to Vioxx, 30-40 percent of which likely resulted in death.[60] He has characterized the public health impacts of Vioxx as perhaps "the single greatest drug safety catastrophe in the history of this country or the history of the world."[61]

### *Searching for Answers*

Observers have strived to identify factors that caused the Vioxx catastrophe. Did FDA approve Vioxx too early?[62] Should Merck have withdrawn the drug earlier, based on the cardiac risks apparent in the VIGOR trial data?[63] Has the culture within FDA become so closely aligned with the pharmaceutical industry that senior management disregards the concerns of its own drug safety experts?[64] Does the fact that authority to withdraw drugs from the market resides in the Office of New Drugs, the same office that approves a new drug as safe for market in the first place, present an inherent conflict of interest?[65]

The full explanation for the Vioxx tragedy likely lies in some combination of these and other theories. This paper, however, will focus on one string in the multi-knotted tangle that is Vioxx: the reasons for, and impacts of the mismatch in resources between the two sides of FDA's drug safety responsibilities – new drug approval reviews on the one hand, and post-market safety monitoring on the other. An examination of selected historical events, trends and pressures that have shaped FDA will illuminate the agency's critical role in protecting the public health, and the rationale for the current

requirement that new drugs be approved by FDA before they are marketed.

The agency's pre-market approval requirements have spurred a constant campaign by industry and aligned conservative interests to minimize the agency's interference with the drug market. Perhaps the most successful tactic deployed in this pursuit has been direct, targeted industry funding of FDA's new drug approval functions. Industry agreed to pay "user fees" to FDA on the condition that the money be used only to supplement appropriated funds for new drug reviews. As intended, the program has led to significant reductions in the time it takes FDA to approve new drugs for market.

More drugs being approved for entry onto the market more quickly than ever meant more demands on the FDA's post-market safety reviewers. As user fees and appropriated funds have continued to flow into FDA's new drug approval arm, however, the agency's post-market drug safety functions have suffered stagnating and even decreasing levels of resources. To ensure that user fees were neither used for non-new drug review purposes nor to substitute for appropriated monies for new drug review, PDUFA contained two funding constraints. Fees could be used: 1.) only for new drug reviews; and 2.) only if FDA continued to allocate at least as much money from congressional appropriations to new drug reviews as it had the year the law was passed. Lagging appropriations, however, forced FDA to make cuts in resources for other functions to ensure it could continue to allocate enough appropriated money to new drug reviews. This arrangement left FDA's drug safety division at its weakest just as the public needed it to be more effective than ever.

## Historical Context: Events that Defined the Mission of the Nation's First Consumer Protection Agency

Although its $1.8 billion budget and staff of 10,800 are "small by federal government standards,"[66] FDA's activities have significant impact on Americans. The agency regulates over 1 trillion dollars worth of products, representing one quarter of the U.S. economy – 25 cents out of every dollar spent annually by American consumers.[67] With the exception of meat, poultry, and pesticides[68] FDA is responsible for ensuring the safety of the nation's entire food supply. Other products that fall under FDA's purview include medical devices, radiation-emitting devices (such as televisions and microwaves), vaccines, cosmetics and prescription and non-prescription drugs for both human and animal use.[69] In large part because of the FDA, most Americans take the safety of these products for granted – as one commentator put it, "I've always worried more about the calories in my food than any contaminants."[70]

Conditions did not always allow for such a feeling of security concerning the nation's food and drug supply. An overview of FDA's critical defining moments will help illuminate the critical importance of the agency's mission and provide context to some of the issues surrounding the Vioxx withdrawal.

### Impure Food and Drugs in the 19th Century

The kind of assured reliance on safe, unadulterated food and medicines that, for the most part, characterizes the American perception today was also likely the norm in the country's earliest agrarian days. In simpler economies, when consumers knew the farmer who produced the food, the merchant who sold the goods and the pharmacist who prepared the remedy prescribed by the town physician, there was little opportunity for anonymity or adulteration. However, as the economy progressed toward industrialization, such traditional relationships changed, and as early as 1820, observers feared that "the growing complexity of the marketplace, the loss of localism, the dispersion of neighborhood production, and the resulting anonymity of modern business would encourage fraud and immorality."[71]

'Immorality' is rather a quaint term to describe the tactics employed by food and drug makers at the time. As producers devised creative means of enhancing their profits in the late nineteenth century, outright fraud was commonplace. Most foods were sold by weight, and chemical analyses revealed that an increasingly widespread tactic was to mix cheap ingredients with the advertised good.[72] So, for example, "chocolate" was augmented by, among other substances, wheat flour, potatoes, beans and soap – and in some cases, poisonous red oxide of mercury, which added not only to chocolate's weight but also its color.[73] Wheat flour, used for bread, was cut with adulterants like chalk and ground beans.[74]

The "patent" or "proprietary" medicines serve as a more blatant – and more dangerous – example of products

misleading consumers by their labels. Originally devised in England, "patent" medicines were not, for the most part, actually patented.[75] Rather, the descriptor referred to the secrecy surrounding the formulas of the potions – neither doctors nor their patients were permitted to know the secret ingredients of the concoctions.[76] Alternately, the "patent" referred to a patent or trademark held not on the key medicine or formula of the concoction, but instead on the distinctive shape of the bottle and/or box the medicine came in, the type styles and pictures on the labels, and associated advertising materials such as display posters.[77] Just as patent protection was sought for promotional materials rather than the chemical formulae of these "quack medicines" and "nostrums," it was their packaging and marketing rather than their medicinal value that secured their success.[78] Factors such as lower postal rates (which made possible the first "direct mail" campaigns), increased national circulation of newspapers and "the spirit of therapeutic laissez-faire in a democratic age" all combined to broaden the market for patent medicines.[79]

The claims of these packaged remedies, which, in the seventeenth and eighteenth centuries had remained "relatively modest and narrow," became "florid and aggressive" by the late nineteenth century.[80] Swaim's "Panacea," for example, was promoted as being able to remedy ulcers, venereal diseases,[81] "cancer, scrofula, rheumatism, gout, hepatitis and syphilis."[82] While colorful, such claims presented very real dangers to customers who actually suffered from diseases and sought out the potions thinking they would provide the cure. Swaim's Panacea, for example, contained three primary ingredients. The first two – sasparilla and oil of wintergreen – were at best ineffective at curing the diseases that Swaim's claimed to treat.[83] The third, corrosive sublimate, the "most rigorous form of medical mercury" was affirmatively harmful, particularly because Swaim's Panacea was also promoted as a cure for mercurial poisoning.[84]

Other particularly vile examples of the patent medicine "quackery" include the narcotic patent medicines – powders to treat congestion that contained cocaine, and soothing syrups made of opium, the latter often given to soothe colicky infants.[85] As historian James Harvey Young observes:

> Nothing could be more cruel than the fastening of this insidious monster on the backs of innocent men, women and children. To make things worse, the disease often became more serious while the patient, his pain deadened by the narcotic, acquired a false impression that he was on the road to recovery.[86]

## The Food and Drugs Act of 1906

Although some six decades of relevant background and nearly three decades of Congressional consideration preceded the Food and Drugs Act of 1906,[87] it was during the Progressive era that forces converged to successfully pass the first federal law to address the safety of the nation's food and drug supply. In 1883, Harvey Washington Wiley, an aspiring young chemist, was invited to Washington, DC to become the Agriculture Department's chief chemist.[88] Wiley made the rising concern about food purity his primary mission at the Division of Chemistry, "applying his technical abilities to illuminating the problem and his political talents to achieving a protective law."[89] As the end of the nineteenth century approached, Wiley joined the progressive movement.[90] While the populists before them had built a movement on railing against the modern industrial state, the progressives were not opposed to the industrial future, but believed that government should curb the excesses of robber-baron capitalism and "answer the grievances of the common man, not the influential man."[91] President Theodore Roosevelt, known for his own progressive ideas, helped Wiley to secure Congressional hearings and, by 1902, funds for experiments on food and drug safety.[92]

Wiley's experiment, dubbed the "poison squad" by a reporter for the *Washington Post*, sought to determine the effect on human health of preservatives then commonly used in foods including, for example, formaldehyde.[93] Volunteers ate preservative-free meals for ten days, followed by a gradual introduction of the preservative under study.[94] Though flawed by modern scientific standards, the experiments demonstrated the deleterious effects of the substances to which the American public was routinely exposed.[95] Still, proposed legislation languished in Congress.[96]

"Muckraking" journalism began to turn the tide. *Collier's*, for example, ran a series of six articles detailing the frauds

and dangers inherent in patent medicines from October 1905 through February 1906.[97] Bolstered by the public outcry the exposé had engendered, Dr. Wiley again approached President Roosevelt, who agreed to support a food and drug bill, and so declared in his State of the Union Speech in December 1905.[98] Within days of the last installment of the *Collier's* series, Upton Sinclair's novel *The Jungle* was released. Sinclair's lurid accounts of the filthy conditions and unsanitary practices in Chicago's meatpacking plants were confirmed by the skeptical President Roosevelt's own investigative team.[99]

These exposés, the public outrage they evoked, and the president's avowed support for food and drug legislation combined finally to create the conditions allowing for passage of the Food and Drug Act of 1906. With regard to drugs, the law required disclosure if a medication contained alcohol, opium, cocaine, morphine and several other notoriously harmful ingredients, and required that any statement on the label regarding a medicine's contents must be true.[100] However, a provision that would have required a full list of ingredients was eliminated from the draft legislation as too controversial.[101] Food could not be "adulterated" or "misbranded" according to the terms of the new law.[102]

Congress did not authorize any funds for Wiley's Bureau of Chemistry to enforce the law, nor did it authorize administrative determination that the law had been violated – rather, it required the government take each offender to court to prove that each particular food or drug was adulterated or mislabeled.[103] Despite its weaknesses, which would be incrementally corrected in the decades to come, the law marked a sea change in policy –it amounted to a declaration that government's role was "to protect citizens from some kinds of commerce rather than just to protect commerce."[104] As Roosevelt biographer Edmund Morris mused, at the conclusion of the fifty-ninth Congress, the President could be proud of his legislative successes, including the Food and Drugs Act, which affirmed a guiding principle of progressivism: "[s]ociety cannot exist unless a controlling power upon will and appetite be placed somewhere."[105]

## Reacting to Public Health Tragedies: Increasing Federal Authority

### *Elixir Sulfanilamide and the Food, Drug and Cosmetic Act of 1938*

The Bureau of Chemistry, officially renamed the Food and Drug Administration in 1927, struggled to do what it could under the parameters of the 1906 law.[106] However, by the 1930s, the agency found itself confronted on the one hand by an inability to effectively regulate products ostensibly covered by the Food and Drugs Act, and on the other hand by products that had not existed when the law was enacted.[107] Cosmetics, for example, increasingly popular and intended to be applied directly to the skin, by then comprised a substantial market.[108] As long as their manufacturers didn't claim some therapeutic benefit on a product label, the Food and Drugs Act did not apply to cosmetics.[109] Some posed significant dangers – for example, Lash Lure mascara caused massive swelling of the eyelids and ulceration of the eyeballs.[110]

*The Food and Drugs Act of 1906 marked a sea change in policy –it amounted to a declaration that government's role was 'to protect citizens from some kinds of commerce rather than just to protect commerce.'*

Without any kind of pre-market approval requirements for medicines, the basic structure of the market that had existed before the 1906 law remained – in short, "damage first, review later."[111] As Franklin D. Roosevelt focused on passing recovery legislation aimed at rehabilitating the country after the Great Depression during his first 100 days in office, one of his so-called "brain trust" of university professors had identified food and drug safety as one of his personal priorities. Rexford G. Tugwell, an economics professor at Columbia University, believed that a pure market in food and drugs would "permit the killing of citizens first, with investigations to follow, and action last, with the result that people were simply not protected."[112] In 1933, just days after Franklin D. Roosevelt's inauguration, Tugwell met with then FDA Commissioner Walter Campbell and discussed some of the shortcomings of the Food and Drugs Act.[113] That very afternoon, Tugwell summoned Commissioner Campbell to his office and said he had repeated the conversation to President Roosevelt, "who authorized a revision of the Food and Drugs Act."[114]

The team assembled by Tugwell concluded that mere amendments could not cure the failures of the 1906 law – although some of its language might be retained, an entirely new law was necessary.[115] The draft legislation would: 1.) prohibit misstatements in advertising beyond just the product label; 2.) require all ingredients to be listed on the product package; 3.) prohibit companies from claiming products would "cure" specified illnesses (including cancer and diabetes); and 4.) require that any proposed new drug be submitted to FDA, along with accompanying information demonstrating product safety.[116] Trade groups such as the Proprietary Association opposed the bill because its members, the patent medicine makers, continued to enjoy a booming trade based on the ability to keep their products' ingredients secret and to proclaim they "cured" a wide variety of diseases.[117] Such opposition kept the bill bogged down for years, and by 1937, the bill's prospects looked dim.[118]

That year the Massengill Company would unintentionally provide the impetus for Congress finally to pass the bill. The company had begun marketing the antibiotic sulfanilamide.[119] While effective at treating a host of bacterial infections, company salesmen reported that many patients would prefer if the bad-tasting medicine came in a more palatable medium.[120] After testing it for appearance, fragrance and flavor – but not safety – the company's chief chemist settled upon diethylene glycol as a solvent.[121] The sweet-tasting diethylene glycol is a derivative of mono-ethylene glycol, which is commonly known today as the active ingredient in antifreeze. By November of that year, 107 deaths had been reported, most of them children.[122] The resulting public outcry prompted Congress to resuscitate the quagmired food and drug legislation, restore the stricken provision requiring safety testing prior to new product marketing and to pass the Food, Drug and Cosmetic Act.[123] President Roosevelt signed the Act, one of the last major domestic measures enacted during the New Deal, on June 25, 1938.[124]

### *Thalidomide and the Kefauver-Harris Amendments of 1962*

Price-fixing in the pharmaceutical industry sparked the Congressional hearings that led to the introduction of the next legislative overhaul of the country's food and drug laws,[125] but another public health tragedy precipitated final action. Hearings convened by Senator Estes Kefauver of Tennessee during 1960 and early 1961 resulted in amendments to the 1938 law that would, among other things, require manufacturers to include the generic names of drugs on all labels (whether or not a brand name also appeared) and include warnings about known drug side effects.[126] The proposal would also require FDA to employ scientific methods to consider not only the safety of a drug but also its effectiveness before allowing a drug on the market.[127] Richard Nixon argued against the bill on the grounds that it would continue to erode "individual" liberties and turn more power over to the centralized national bureaucracy.[128] The American Medical Association objected to the bill on the ground that it would interfere with doctors' authority to treat their patients.[129] The drug industry responded by drafting legislation to counter the Kefauver bill.[130]

By the fall of 1961, as the Kefauver bill languished in Congress, reports began to surface about birth defects associated with the use of a drug with the generic name thalidomide.[131] The drug, first marketed in West Germany in 1957, was used as a sleeping aid, a sedative and to treat morning sickness in pregnant women.[132] A year earlier, Richardson-Merrell, Inc. had submitted its application to market thalidomide under the trade name Kevadon in the United States.[133] The FDA's Dr. Frances Oldham Kelsey, assigned to review the materials in support of the application, felt the information submitted by the company was severely lacking, and that the company's unsupported claims were "just glowing, too good to be true."[134] Under the Food, Drug and Cosmetic Act of 1938, if Dr. Kelsey raised no objection to the marketing of the drug within 60 days, the company would be free to sell it to American consumers.[135] Despite incessant pressure from company officials to approve the drug, Dr. Kelsey decided to request more data from Richardson-Merrell.[136] The resulting delay provided FDA, and eventually, the American public with the opportunity to learn of thalidomide's true health effects as they became manifest in the countries that had already allowed the drug onto the market.

"Phocomelia" is a term derived from two Greek words meaning "seal" and "limb" and describes a medical condition that causes babies to be born lacking long bones in the arms and legs.[137] While natural occurrences are extremely rare, hundreds of babies afflicted with the condition began to be born in Germany, where by 1961

a physician suspected the cause to be thalidomide taken by mothers during the first three weeks of pregnancy.[138] Subsequent investigation by a Johns Hopkins University pediatric physician confirmed that thalidomide, initially hailed as safer than most other sedatives, was the reason for the tragic infant deformities.[139] Richardson-Merrell withdrew its application to market the drug from FDA in March 1962.[140]

The number of babies born in Germany and other European countries with deformities caused by thalidomide is estimated conservatively at around 8,000, and an additional 5,000 to 7,000 babies are believed to have died of their deformities before birth.[141] Had FDA's Dr. Kelsey yielded to industry pressure and allowed the drug to be released onto the U.S. market, an estimated 10,000 more deformed babies may have been born before the effects of thalidomide became apparent.[142] When the *Washington Post* publicized her actions in mid-July 1962, a "tidal wave of national publicity" ensued, and President Kennedy presented her with the Gold Medal Award for Distinguished Civilian Service.[143] Public concern about the possibility of other drugs with similarly horrific side effects making it onto the U.S. market prompted Congress to revive the languishing bill proposed by Senator Kefauver, and in October 1962 both houses unanimously passed the Kefauver-Harris Drug Amendments.[144]

The new law provided, among other things, that FDA must approve all plans for clinical testing and that a drug's sponsor was required to demonstrate, by substantial evidence, that the drug was not only safe but also effective.[145] Data submitted to demonstrate effectiveness must have been generated through "adequate and well-controlled studies."[146] Perhaps most importantly, whereas the 1938 law had provided that drugs could be marketed unless the FDA objected within 60 days of being notified of the proposed marketing,[147] the Kefauver-Harris amendments reversed the burden. The pre-market notification system was converted into a pre-market approval system[148] – from then on, companies would have to prove the safety and effectiveness of new drugs in order to earn FDA's approval to enter the market.[149] Significantly, Congress also provided FDA with the authority to withdraw the approval of a drug if new information led the agency to determine that the drug was no longer safe or effective for its intended use.[150]

## So Why Do We Need the FDA?: Pre-market Drug Safety Reviews

History provides concrete examples of harms that resulted from an unregulated market in food and drugs. The structural cause of such historical examples of harm is, at its most basic level, the same today as it was during and before Theodore Roosevelt's time. Simply stated, "the logic of 'profit alone' that dominated the companies in the nineteenth century dominates them today. This is one reason the FDA's job is difficult, and necessary."[151] It was the desire to maximize profits that led food manufacturers to mix cheap chalk into more expensive flour and use formaldehyde to keep food looking fresh for longer. The same motive led the proprietary medicine manufacturers to sell alcohol and opium solutions with claims that they calmed babies and cured cancer. When salesmen suggested that sulfanilamide might sell better if it came in a sweet-tasting syrup, the drug's manufacturer mixed it with a sweet-tasting – and lethal – relative of antifreeze. Because thalidomide promised an edge over other sedatives on the market at the time, companies in Europe and the United States jumped at the chance to sell it to pregnant women suffering from morning sickness after only the most preliminary of safety trials.

Once the hazards caused by dangerous products such as, for example, elixir sulfanilamide and thalidomide become public, consumers would no longer buy the products and demand for them would essentially disappear. However, the noneconomic reason to regulate markets in food and drugs is that harms on the scale of those caused by elixir sulfanilamide and thalidomide are simply unacceptable – as a society, we do not want to wait until thousands of deformed babies are born before market forces eliminate a dangerous product. In sum, "'[l]et the customers decide' or 'let the free market function unfettered' may be acceptable for brooms, but it is unacceptable in the realm of prescription drugs."[152]

This basic, common-sense explanation of why a referee, not motivated by profit, is necessary to protect consumers from disastrous collateral damage is backed up by well-known principles of microeconomic theory. One of the critical assumptions of a functioning market is that participants have all the information necessary to make informed choices. "Asymmetric information" exists

when one side of the market (sellers) know more about a good's quality than do participants on the other side (buyers).[153] In the drug market, full information about chemical compounds is either unavailable or too complex for practical use, with the result that consumers are unable to consider all the necessary information to make informed choices.[154]

## Pre-market Drug Safety Reviews

The FDA protects drug consumers from the effects of unrestrained company profit motives, or corrects the asymmetric information market failure, in two principle ways. First, by requiring companies to adequately test their new products, FDA ensures the generation of information about the safety and effectiveness of new compounds – information that was lacking when thalidomide went on the market, or of which elixir sulfanilamide's manufacturer was unaware when diethylene glycol was chosen as a solvent.[155]

Companies must first perform pre-clinical laboratory and animal tests to preliminarily evaluate a new compound's toxicity and biological activity.[156] Before proceeding to clinical trials involving humans, they are required to submit the results of the preliminary research to FDA in an investigational new drug application (INDA).[157] If FDA does not object within 30 days of submission of an INDA, the drug's sponsor may proceed to a three-phase clinical testing process.[158] Phase I clinical trials involve twenty to eighty patients, and are primarily devoted to evaluating safety.[159] Phase II clinical studies involve 100 to 300 disease-state patients and focus on the drug's effectiveness, side effects and dosing.[160] Phase III trials are performed on drugs that show preliminary evidence of efficacy in the Phase II studies.[161] Additional data on safety and effectiveness are gathered in Phase III clinical trials, which involve 1000 to 3000 disease-state patients.[162] If, after completion of the three clinical trial phases, the data support the drug's safety and efficacy, its sponsor files a New Drug Application (NDA) with the FDA.[163]

Next, by employing doctors, pharmacologists and epidemiologists to review the information submitted by drug sponsors to determine whether it adequately demonstrates that the compound is both safe and effective, FDA acts as the public's expert, interpreting the complex scientific information that would not be useful to the average non-scientist consumer. Data generated during the Phase III studies provide the basis for FDA reviewers to decide whether to approve the drug for its intended use.[164] In making the decision whether or not to grant approval, FDA considers the risk-benefit ratio of the drug. So, for example, FDA may conclude that the overall risk posed by an effective drug is outweighed by a significant potential benefit to the patients the drug is intended to treat.[165]

## Post-market Drug Safety Risks

Even drugs that appear both safe and effective after being subjected to the rigorous three-phase pre-market testing regime may pose dangers that will not emerge until after the drug is on the market. Clinical studies are limited in their ability to detect rare or delayed adverse reactions.[166] The relatively short duration of clinical trials, the small number of patients exposed to the drug during the studies and the carefully controlled environment under which the trials are conducted[167] are all artificial conditions. Since most NDAs include safety data on several hundred to several thousand patients, an adverse event that occurs in one in 5000 or even one in 1000 users may not show up in clinical trials but still pose a serious safety problem once released to market.[168] Further, once on the market, a drug is taken for longer periods of time, often in combination with other prescription drugs and/or lifestyle factors (such as, for example, alcohol use and smoking).[169]

Therefore, although pre-market testing performs the crucial function of generating significant safety information about a new drug before the general public is exposed to it, it cannot identify all the drug's side effects.[170] Specifically, a 1990 Government Accountability Office (GAO) study found that 51 percent of drugs approved by the FDA have serious adverse effects not detected during pre-market studies.[171] Accordingly, as Dr. Raymond Woosley of the University of Arizona has observed, "Americans need to recognize that every time they put a pill in their mouth, especially a new pill they've never taken before, it's an experiment. How big an experiment depends on the pill and how well it's been studied."[172]

## Attacks on FDA's Pre-market Review of New Prescription Drugs

The inverse relationship between the extent to which a new drug has been subjected to pre-market studies and the risk remaining when the drug goes on the market creates the tension that one commentator has termed FDA's "fundamental dilemma":

> In fulfilling its mission to monitor and control the safety and efficacy of drugs, the Agency continually walks a razor's edge between two opposing risks – premature approval of dangerous drugs and undue delay in making safe, effective, and medically useful drugs available to the public.[173]

Seizing upon the idea that, in theory, delay in getting new drugs to market could pose risks to the public, opponents of regulation have argued that FDA can harm consumers just as much as unsafe drugs. As historian James Harvey Young notes:

> Right from the start of new drug evaluation some critics, especially from the drug industry, accused FDA of undue caution and time-consuming deliberateness. Dangers of disaster from rare adverse reactions, it was argued, were being far outweighed by the suffering and death resulting from delays in bringing effective new medications into use.[174]

The argument's pedigree can be traced to two articles published in 1973. The first, by Dr. William Wardell,[175] was inspired by his observations while practicing in Australia and England that some drugs available in those countries were not available in the United States.[176] Inspired to look into the issue further, Wardell found that of the 180 new drugs that appeared in Britain and the U.S. from 1962 through 1971, 43 were introduced in Britain first, while only 39 were introduced in the U.S. first or simultaneously.[177] Britain's modest edge in the comparison provided fuel for what would become a major controversy over a so-called "drug lag."

Although Dr. Wardell did not attribute "drug lag" to FDA regulations, conservatives seized upon the idea as proof that the FDA was the root of a host of evils. Economist Sam Peltzman aggressively went where Dr. Wardell had not, asserting in no uncertain terms that the Kefauver-Harris amendments and FDA regulation imposed costs in the form of "forcing consumers to forgo benefits from effective new drugs" that far outweighed any benefits.[178] Despite numerous unanswered questions and methodological flaws in these two articles,[179] their message was seized upon by opponents of regulation.

In 1977, Congress asked the General Accounting Office (GAO) to conduct an investigation of the FDA's drug approval process.[180] The 1980 report concluded that FDA took an average of seventeen months to review NDAs, and that out of six countries studied, the United States and Sweden took the longest time to approve new drugs.[181] However, far from confirming the conservative theory that the delay in processing new drug applications resulted purely from an unduly burdensome regulatory scheme, the GAO report declared that, "[b]oth FDA and the drug industry contribute to the length of the drug approval process and both need to work to speed it up."[182] Specifically, while the GAO recommended that FDA "make its process more efficient and responsive,"[183] it also advised pharmaceutical companies to "commit themselves to speeding up the process by submitting complete NDAs and promptly resolving deficiencies FDA identifies."[184]

The GAO report also highlighted the importance that the lack of sufficient resources at FDA played in the "drug lag" problem, noting that "[b]ecause of other demands on their time, reviewers spent an average of less than 40 percent of their time reviewing NDAs . . . . According to FDA, review time could be shortened if reviewers could spend more time reviewing NDAs."[185] Indeed, as FDA's role changed over the years from "policeman to gatekeeper," its responsibilities increased and so did the demands on its budget and workforce,[186] but Congress failed to match FDA's expanded mandate with sufficiently expanded funding.[187]

## Reforms, and Continuing Attacks

### *FDA Reforms to Respond to the AIDS Epidemic*

Working within its budget constraints, FDA did what it could to address legitimate concerns over delays in access to truly lifesaving drugs. In an illustration of what Professor Margaret Gilhooley has called the agency's adaptive role, FDA instituted important reforms in response to a new epidemic.[188] Acquired Immune Deficiency Syndrome (AIDS) first manifested in 1981

as opportunistic infections, pneumonia and cancer resulting from its debilitation of the human immune system.[189] By 1988, the disease had racked up a death toll of 41,000.[190] From 1981 through 1987, there were no drugs approved to treat AIDS.[191] Anger and frustration at the lack of treatment options for victims of the epidemic were directed at FDA,[192] despite the fact that, as FDA Commissioner Frank Young reminded, the agency did not develop new drugs, but was a "passive conduit" through which drugs passed for review when submitted by sponsors.[193] Indeed, AIDS posed an unprecedented challenge to drug manufacturers, and only in 1984 did the first promising compound emerge. Originally developed as a cancer treatment, azidothymidine (AZT) was submitted by Burroughs-Wellcome in response to the National Cancer Institute's call for existing drugs that might be effective in treating AIDS.[194]

*As FDA's role changed over the years from 'policeman to gatekeeper,' its responsibilities increased and so did the demands on its budget and workforce, but Congress failed to match FDA's expanded mandate with sufficiently expanded funding.*

FDA took important actions to speed access to AZT. In 1987, the agency codified its policy of allowing investigational new drugs (INDs) to be used in treatment of "serious or immediately life-threatening disease conditions in patients for whom no comparable or satisfactory alternative drug or other therapy is available."[195] Nearly 5000 AIDS patients received AZT prior to FDA approval.[196] In 1988, the agency issued regulations allowing for accelerated ("fast track") review of drugs for life-threatening and severely debilitating illnesses, which it had first employed on an ad hoc basis for AZT.[197] The procedures allow provisional approval of certain drugs after only two, rather than the usual three, phases of human testing.[198] As a result, FDA's approval of AZT was six years faster than typical contemporary approvals.[199] By the late 1990s, FDA's fast track allowed for even more rapid approval of significantly more effective protease inhibitor treatments for HIV and AIDS.[200]

### *The Prescription Drug User Fee Act of 1992*

While the FDA's IND and fast track initiatives were critical in promoting faster access to treatments for "serious or immediately life-threatening disease conditions" such as AIDS, the systemic problem of inadequate funding remained. In 1992, FDA Commissioner David A. Kessler told Congress that, due to the chronic inadequacy of funding from general revenues, it was time to look "very seriously" at a proposal that had first been advanced 20 years earlier: user fees.[201] In a 1971 report, the GAO had recommended charging the prescription drug industry user fees in conjunction with its review of NDAs.[202] Initially, the proposal was deemed unworkable due to the peculiarities of the law under which the fees would have been assessed.[203] However, faced with mounting budget deficits, the Reagan Administration proposed user fees in its budgets for 1985 and 1986.[204] The pharmaceutical industry objected to the proposals on the ground that, as configured, the user fees would have substituted for revenues appropriated for FDA from general funds.[205] Such an arrangement would have resulted in no net increase in resources for FDA (and therefore no increase in the speed with which FDA was able to process NDAs).[206]

As FDA and congressional staff worked to develop draft user fee legislation in 1992, the pharmaceutical industry indicated it would support user fees if the fees would: 1.) augment, not substitute for, appropriated monies for new drug reviews; 2.) be fully dedicated to new drug reviews; and 3.) be based on commitments by FDA to specific improvements in the approval process.[207] Negotiations among FDA, industry and members of Congress resulted in a proposal that specified that fees could be used only for new drug reviews. Although necessary, that restriction would not be sufficient to satisfy industry's other condition – that user fees augment, not substitute for, appropriated funds for new drug reviews. To address that concern, the legislation stipulated that in order to spend the user fees collected in a given year, FDA would have to show it had spent the same amount of appropriated monies on new drug reviews as it had in 1992 (adjusted for inflation).[208] Another aspect of the user fee program, not spelled out in the draft legislation but "critical in eliciting manufacturer support" were performance goals for speeding new drug approval, which are memorialized in correspondence from FDA to the relevant House and Senate committees.[209]

Over the objections of some of the more resolute conservatives in the White House, who maintained that it wasn't lack of funding at FDA that resulted in the agency's "gridlock,"[210] President George H.W. Bush signed the Prescription Drug User Fee Act (PDUFA) into law on October 29, 1992.[211] The user fee program was authorized for five years, "with the understanding that FDA's success in meeting its announced goals would be decisive in assessing any renewal."[212] In 1995, Commissioner Kessler reported that FDA was well on its way to achieving its performance goals.[213]

### *The FDA Modernization Act of 1997*

Even with FDA on-track toward fulfilling its PDUFA commitments, the agency became a prime target for the caustic deregulatory rhetoric that accompanied the Gingrich revolution. Speaker Gingrich described FDA as "the leading job killer in America," and called Commissioner Kessler (who had been appointed by President George H. W. Bush) a "thug and a bully."[214] Conservative groups – beneficiaries of donations from the pharmaceutical and medical device industries – fed and echoed Gingrich's rhetoric.[215] The Washington Legal Foundation (WLF) ran advertisements in the *New York Times*, *Wall Street Journal* and other newspapers that showed tombstones in a graveyard and proclaimed:

> If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious . . . . The problem with health care in America is the FDA.[216]

The Progress and Freedom Foundation proposed FDA's drug and medical device approval functions be turned over to private research groups or universities, and the Competitive Enterprise Institute advocated removing FDA's "monopoly" by removing its pre-market approval authority.[217] The rationales for the deregulatory proposals sounded in Sam Peltzman's 1973 critique, which had argued that the sole purpose of the 1962 Kefauver-Harris amendments was to prevent tragedies on the scale of thalidomide and that the benefits associated with avoiding such outcomes fell far short of costs in the form of delayed access to new drugs:

> Entities regulated by the FDA . . . face a zero-risk, "better safe than sorry" culture in which action (or inaction) is taken more out of a fear of the unknown than respect and appreciation of the known. A certain degree of institutional risk aversion is understandable given that the FDA's historical mission has been to place consumer health above (and perhaps even to the exclusion of) all other considerations. . . . When the costs of excessive caution are factored in – not only lost profits, jobs, and foregone research and development, but, more importantly, lost lives that could have benefited from products frozen in the FDA queue – the net effect to the American consumer arguably is negative, not positive.[218]

According to the proponents of "privatization," incentives at FDA were skewed to encourage drug reviewers to disapprove new drugs. Whereas approving a drug that later caused serious adverse events would result in high-profile "congressional examination" and "professional criticism," a non-approval or delayed approval of a new drug "typically slips into obscurity."[219] Thus, the argument went, the only way to fix the FDA's culture of "risk avoidance" and "autocratic style of regulation" would be to break "FDA's regulatory monopoly and permit[ ] third parties to participate in a competitive market for product review."[220]

Critics skewed the facts in order to come up with specific examples of instances in which FDA had unnecessarily slowed the approval of a drug or device that could have saved lives.[221] The WLF, for example, in its advertisement lambasting FDA against a backdrop of tombstones, asserted that "[d]uring the seven years it took to approve tacrine, thousands of Alzheimer's patients gradually lost their memories. Nobody knows how many died."[222]

The real story paints quite a different picture. In 1986, the New England Journal of Medicine published a study that appeared to demonstrate dramatic improvements in Alzheimer's patients treated with tacrine.[223] The widely publicized study, which sparked hope among victims of Alzheimer's and their families, later came under question as to its design and the way it was conducted.[224] Subsequent studies, including two considered by the FDA's Peripheral and Central Nervous System Drugs Committee in 1991, offered significantly less convincing evidence of tacrine's effectiveness.[225] The advisory panel ultimately concluded that the equivocal evidence of effectiveness did not outweigh the drug's risk of liver

toxicity, and recommended against FDA approval.[226] Warner-Lambert, the drug's sponsor, bemoaned the recommendation, stating that it would result in denial of the drug to "a large population that has no other treatment," for "another year and a half to two years."[227]

FDA, however, opted to expand access to tacrine for Alzheimer's patients under its treatment IND regulations, which had been promulgated to speed access to experimental treatments for AIDS.[228] Alzheimer's advocates welcomed FDA's recommendation.[229] Warner-Lambert, which had decried the advisory panel's decision a week earlier on the ground that it would keep patients from needed therapy, initially hedged on whether it would adopt FDA's recommendation.[230] (Under the treatment IND regulations, companies must either provide experimental drugs for free or charge only the amount necessary to cover costs.)[231] Ultimately, Warner-Lambert did participate in the program, and over 7,400 patients had received tacrine by the time FDA approved it in 1993 on the basis of the additional data the 1991 advisory panel had requested.[232]

Even more insidious WLF's misrepresentation of FDA's actions was its suggestion that earlier approval of tacrine may have prevented the deaths of "who knows how many" Alzheimer's patients. Tacrine is not a cure for Alzheimer's disease, nor will it stop the disease from progressing.[233] Rather, it can help slow the breakdown of acetylcholine (ACh), a neurotransmitter believed to be important for memory and thinking.[234] As Alzheimer's disease progresses, however, the brain produces less and less ACh, so tacrine eventually loses effectiveness.[235]

Congressional hearings similarly failed to reveal the supposed cadre of life-saving drugs being held at bay by the foot-dragging, overly cautious bureaucrats at FDA.[236] Ultimately, the sweeping deregulatory reforms proposed in the Progress and Freedom Foundation's *Advancing Medical Innovation: Health, Safety and the Role of Government in the 21st Century*[237] failed to translate into legislation. According to the proposal's authors,

> In its current form, the Food and Drug Administration is a prototypical centralized, bureaucratic regulatory agency, similar to so many other agencies designed during the heyday of the Progressive era. By modern standards, it is cumbersome, slow, expensive and inefficient.[238]

Yet the principal proposal to make "modern" the outmoded FDA was a throwback to pre-1962 conditions when, unless the FDA objected, a drug went to market. The conservative think-tank advocated reforming the approval process to allow manufacturers to market a new drug provided: 1.) they had hired a commercial service to review it; and 2.) FDA failed to object on the ground that the drug was unsafe or ineffective.[239]

In 1997, Congress reauthorized the user fee program, including the stipulations that the fees would only be available for new drug reviews,[240] and only if FDA continued to allocate appropriated monies to new drug reviews at or above 1997 levels (adjusted for inflation).[241] Renewal of PDUFA in 1997 also provided the conduit for several FDA reforms,[242] albeit significantly scaled down from the vision propounded by the Progress & Freedom Foundation and its allies. Notable provisions of the FDA Modernization Act of 1997 (FDAMA) include: 1.) discrete options for third-party review of low- to moderate-risk medical devices;[243] 2.) codification of FDA regulations allowing for fast track approval of certain drugs; and 3.) a more interactive process for the approval of NDAs.[244] Through requirements that FDA meet with drug sponsors "for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim,"[245] FDAMA sought "to alter the historically adversarial relationship between pharmaceutical companies and the FDA."[246]

## The Other Side of FDA's 'Fundamental Dilemma': Premature Approval of Dangerous Drugs

### Safety-Based Drug Withdrawals in the Wake of PDUFA

Although Vioxx is the most recent safety-based drug withdrawal, it is by no means the first. The same year Congress passed the FDAMA and reauthorized PDUFA, FDA asked the makers of Redux (dexfenfluramine) and Pondimin (fenfluramine) – two wildly popular diet drugs – to withdraw their products from the market.[247] FDA approved Pondimin in 1973 as an appetite suppressant for the short-term management of obesity,[248] but the drug's popularity (and thus, use) was limited by the drowsiness it caused.[249] In 1996, FDA approved Redux, also for the short-term management of obesity.[250]

Though a chemical relative of Pondimin, Redux did not share the side effect of pronounced drowsiness.[251] Some physicians prescribed one or the other of the "fen" drugs in combination with another appetite suppressant, phentermine, often for use in long-term weight loss programs.[252] The "fen" of the popular "fen-phen" diet drug craze was later identified as the causative agent in significantly elevated risks of valvular heart disease among patients taking the medication.[253] Before Redux was withdrawn, an estimated six million patients took fen-phen.[254] Before and after it withdrew Redux from the market, FDA received reports that identified the drug as a suspect in 123 deaths.[255]

*Whereas years of deregulatory rhetoric had charged FDA with excessive delay in getting drugs to market, a rash of safety-based drug withdrawals between 1997 and 2001 refocused attention on the dangers inherent in premature approval of dangerous drugs.*

Over the next few years, a string of additional safety-based drug withdrawals followed. (*See* Appendix.) Duract, a painkiller approved in 1997 was withdrawn less than a year later after four patients died and eight others required liver transplants.[256] Clinical trial data submitted to FDA as part of Duract's NDA demonstrated sufficiently high risks of liver toxicity, which increased as the length of treatment increased, to prompt the reviewing medical officers to recommend a black box warning.[257] A black-box warning, however, would put Duract at a competitive disadvantage – especially since there were already 20 prescription and over-the-counter painkillers on the market.[258] Wyeth-Ayerst (the drug's sponsor) approached the reviewers' superiors, and in July 1997, when the drug was approved, the label did not include a black box.[259] Instead, in fine print, the label recommended that Duract be used for "generally less than 10 days."[260] Seven months after FDA approved the drug, after receiving reports of severe liver damage, Wyeth added a black box to the Duract label.[261] Now the warning was unequivocal – the drug should not be prescribed for longer than ten days.[262] By June 1998, as reports of "severe injuries and death with long term use of Duract" continued to roll in, Wyeth withdrew the drug.[263] By late that year, FDA had received reports citing the painkiller as a suspect in 68 deaths, 17 of which involved liver failure.[264]

Posicor, a treatment for high blood pressure and symptomatic chest pain, was also approved in 1997 and withdrawn in 1998.[265] When FDA's Cardiovascular and Renal Drugs Advisory Committee met to discuss whether to recommend approval of Posicor, it knew that one man had suffered "sudden death" in one study of the drug, and that another 142 patients had died suddenly during another study, after treatment with either Posicor or a placebo.[266] Because the study was still underway, the drug's manufacturer, Hoffman-La Roche, elected to keep the details sealed for confidentiality reasons.[267] "This left FDA officials a choice: Wait a year or more, or approve Posicor without knowing the details."[268] One member of the advisory committee reasoned that since there were numerous other effective blood pressure medications on the market, "why not be safe with the public?"[269] His view was that of the minority, however – the committee voted 5 to 3 to recommend approval of Posicor.[270] On June 20, 1997, FDA followed the committee's recommendation and approved the drug.[271] Just under one year later, Roche announced it was withdrawing Posicor, based on "evolving information concerning the potential for drug interactions" and "preliminary results" from the study that had concerned members of the advisory committee.[272]

In July 1993, FDA approved Propulsid, a drug to treat nighttime heartburn.[273] Electrocardiograms submitted with the NDA included a troubling indicator – the drug prolonged patients' "'QT interval,' the time during which the heart's main pumping chambers contract and then relax."[274] Even slight increases in the QT interval can trigger a heart rhythm abnormality called an arrhythmia, which can cause sudden death.[275] The warning may have been caught had FDA's cardiac specialists been involved in the review, but it was the GI drug division that had reviewed Propulsid's NDA.[276] Once on the market, pediatricians began to prescribe Propulsid for treatment of gastric reflux in infants although FDA had not approved it for that indication.[277] By August 1997, the agency knew the drug had been cited as a suspect in "at least" three deaths among child patients, and requested that the product label be changed to "contraindicate," or

warn against, use in infants.[278] Only in June 1998, however, did the manufacturer agree with FDA on a label containing the contraindication.[279] In March 2000, FDA announced the withdrawal from the market of Propulsid, which by then had been linked to 341 reports of heart rhythm abnormalities and 80 reports of deaths.[280]

Baycol was one of the class of statin drugs, which lower levels of cholesterol by blocking an enzyme required in its synthesis.[281] When FDA approved it in 1997, it appeared, like the other statins, to promise lifesaving benefits, while causing few side effects.[282] Baycol, however, would prove different. From the beginning, the statins were known to cause a rare muscle disorder called rhabdomyolysis.[283] Patients affected with the condition experience a breakdown of muscle tissue, which floods the kidneys with cellular waste.[284] If the kidneys become overwhelmed and shut down, death occurs.[285] Baycol has since been linked to the disorder at a rate about ten times as high as that associated with the other statins.[286] By 1999, several reports on rhabdomyolysis associated with Baycol use had come in, and FDA and the drug's manufacturer issued undertook a series of warnings to communicate how best to minimize the risk of developing the condition.[287] The warnings appear to have failed – in August 2001, after reports of deaths linked to Baycol continued to come in, its manufacturer pulled it from the market.[288] In its four years on the market, the drug was associated with 31 deaths.[289]

In all, 13 drugs approved by FDA were withdrawn from the market for safety reasons between 1997 and 2001.[290] In contrast, during the 20-year period between 1974 and 1993, only ten FDA-approved drugs were withdrawn from the U.S. market for safety reasons.[291] The increase in number of withdrawals is due in part to a larger number of drugs on the market. Because the majority of withdrawals during this time period were of drugs approved by FDA after the user fee program was instituted, however, the pattern caused concern. Public attention now focused on the other side of FDA's "fundamental dilemma" – whereas years of deregulatory rhetoric had charged FDA with excessive delay in getting drugs to market, the rash of drug withdrawals highlighted the dangers inherent in premature approval of dangerous drugs. Observers asked, "have increases in the speed of new-drug review had an adverse effect on new-drug safety?"[292] Professor Mary Olson of the Yale University School of Public Health examined the question using statistical analysis of empirical data and concluded, "reductions in new-drug review times are associated with increases in both [adverse drug reactions (ADRs)] requiring hospitalization and ADRs resulting in death."[293]

## *Speeding Up Drug Approvals Means Increased Post-market Risks*

As its proponents intended, PDUFA leads to decreased drug review times in several ways. First, the user fees provide an influx of resources to the FDA division responsible for reviewing new drug applications.[294] Second, because PDUFA has a fixed term, renewal of the user fee program provides a tremendous incentive for FDA to achieve the performance goals it committed to in exchange for the fees – 12 months for most drugs, which represents a significant decrease from the 31-month average review time between 1990 and 1992.[295] Finally, PDUFA's requirements that FDA prepare annual performance and financial reports, used for oversight and evaluation, help to ensure the agency stays on track toward achieving its performance goals.[296]

FDA officials point out that the rise in the number of newly approved drugs entering the market, combined with greater public consumption of medicines, increases the probability of misprescribing and adverse effects.[297] Moreover, reductions in review times can mean the risks posed by new drugs once they reach the market are greater due to both reduced scrutiny during the review process, and also less foreign marketing data.[298] An unintended safety benefit of the so-called "drug lag" to American consumers was the information generated about drugs that were marketed first in other countries.[299] Foreign data had alerted Dr. Kelsey to the dangers of thalidomide and were thus instrumental in preventing the drug's entry onto the U.S. market. Under current law, drug sponsors must provide foreign data, if available, to FDA along with their NDAs.[300] Accordingly, for drugs already approved elsewhere, FDA can base its review not only on clinical trial data but also real-world data bearing on the drug's side effects.[301]

## So Why Do We Need the FDA?: Post-market Safety Monitoring

### Inadequate Industry Incentives

The Pharmaceutical Research and Manufacturers of America (PhRMA), a lobbying group that represents the country's leading drug companies, argues that companies maintain their own post-market safety monitoring divisions and have a long history of proactive safety surveillance.[302] But drug companies invest enormous amounts of time and money in developing drugs. Therefore, companies confronted with data suggesting unexpected safety risks associated with a drug face "an almost insurmountable conflict of interest" in evaluating whether and when to withdraw it.[303] Stated more directly, "pharmaceutical manufacturers would prefer to ignore red flags signaling problems with a product in order to keep the product on the market."[304] The conflict is evident in, for example, Merck's delay in including warnings based on the VIGOR study on the Vioxx product label – Merck's primary concern was the $500 million drop in sales it projected if the information was added to the more urgent "warnings" section of the product label.[305] During the nearly two years the company spent negotiating with FDA to avoid that outcome, physicians and consumers were deprived of critical safety information about the drug.[306]

Also according to PhRMA, the threat of personal injury liability serves as an incentive for the industry to engage in vigilant post-market safety monitoring.[307] Vioxx serves as a powerful example of the scale of potential liability exposure for injuries caused by prescription drugs. Merck faces a total of at least 4,100 personal injury suits and a host of class-action suits.[308] The company's stock has fallen about 38 percent since it pulled Vioxx off the market.[309] The outcome of the first Vioxx trial appears to confirm investor concerns: in August 2005, a Texas jury awarded the widow of a Vioxx user $253 million in damages.[310] A Texas law capping punitive damages will reduce the award to about $26.1 million.[311]

Tort "reformers" are actively working to undermine the liability incentive. Legislation proposed in the 109th Congress would completely eliminate punitive damages nationwide for most lawsuits based on injuries caused by prescription drugs.[312] The proposed bill would prevent punitive damage awards against manufacturers for injuries caused by products that were subject to premarket approval – and approved – by the FDA,[313] despite the fact that FDA cannot know all a drug's safety risks prior to deciding whether or not to approve a drug.[314] PhRMA, which is concerned with and active on a variety of issues facing Capitol Hill, earmarked $72.7 million for all its federal lobbying efforts in 2003.[315] While pointing to the threat of liability as an incentive for drug companies to "address all safety considerations promptly,"[316] PhRMA is certainly aware of the legislation that proposes to essentially eliminate that very incentive.[317]

### Broken Promises: Phase IV Clinical Trial Commitments

Experience with semi-voluntary industry efforts adds evidence to the case for an independent drug safety monitor. For some drugs, FDA may condition its approval on the sponsor's agreement to engage in post-marketing (Phase IV) studies to evaluate long-term safety and effectiveness.[318] FDA may request Phase IV studies in cases where the drug under review appears, from pre-market testing data, to be both safe and effective, but where FDA staff believe unanswered questions remain concerning information that may need to be included on the product label to ensure proper prescription and use.[319]

Each year the FDA publishes a report on the status of sponsors' Phase IV commitments in the Federal Register.[320] FDA's 2005 report indicated that of the close to 1,200 such studies committed to by drug companies, nearly 70 percent have not yet begun.[321] Although FDA has the authority to revoke approval for some drugs for which Phase IV commitments have not been honored, the agency has not invoked that authority, "nor is it clear that to do so would be in the best interest of patients."[322] Thus, "the upshot is that FDA depends on companies for post-market safety studies but has no legal authority to force firms to do them."[323]

The only sanctions the FDA is authorized to levy on manufacturers that have failed to honor Phase IV commitments are to: 1.) publish a statement on the FDA website stating a study was not completed (and if the reasons for failure to complete the study were not satisfactory, a statement to that effect);[324] and 2.) require the drug's sponsor to notify doctors of its failure to complete the Phase IV study, along with any questions

regarding the drug's benefit or safety that remain as the result of the failure to complete the study.[325]

## FDA's Post-market Drug Safety Monitoring

Whether or not Phase IV studies are requested (or performed) for a given drug approved by FDA, the agency's primary means of monitoring the safety of prescription drugs once they enter the market is through adverse event reporting. An adverse event is "any undesirable experience associated with the use of a medical product in a patient."[326] FDA monitors adverse drug events through a system of mandatory reporting by manufacturers and voluntary reporting by health care professionals.[327] Specifically, manufacturers are not required to seek out safety information about their products, but must file a report with FDA upon being notified by a health care professional or consumer of "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug-related."[328] Adverse drug experiences that are "serious" and "unexpected" must be reported to FDA within fifteen days.[329] Because drug manufacturers are required to submit to FDA reports that health care professionals submit to them voluntarily, the "mandatory" system is "only as effective as the degree of voluntary participation permits."[330]

The FDA's voluntary Safety Information and Adverse Event Reporting Program, "MedWatch," provides a direct route for "healthcare professionals and consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use."[331] The MedWatch system allows voluntary reporting of adverse events directly to FDA via mail, phone, fax or the internet.[332]

Significant shortcomings render the both reporting systems incapable of quickly and effectively identifying serious and unexpected side effects of new drugs. The number of voluntarily reported adverse events represents only a small fraction of actual adverse drug events – the "proverbial tip of the iceberg."[333] Specifically, epidemiologists estimate that voluntary reporting captures only 10 percent of adverse events.[334] According to one study, the proportion of serious adverse events reported to FDA is even lower – about 1 percent.[335] Among the factors contributing to the low reporting rate for adverse events is that when confronted with an unexpected outcome of treatment, physicians may not consider it to be drug-induced, but instead deem the event related to the course of the underlying disease.[336] This limitation of the system becomes an even greater impediment to accurate reporting when the serious side effects are already common in the population – such as the heart attacks and strokes linked to Vioxx and the other COX-2 inhibitors.[337] Spontaneous reporting, therefore, "provides only a fraction of information required to develop programs to protect the public from the health risks of marketed drugs."[338]

Recommendations for improving the effectiveness of FDA's post-market drug safety programs have been made for years. In 1993, following the withdrawal of Redux and Pondimin, Thomas J. Moore, Dr. Bruce Psaty and Dr. Curt Furberg suggested that, in addition to seeking to identify new adverse drug reactions, FDA need expand its focus to include: 1.) estimating the number and cause of serious injuries and deaths; 2.) monitoring the effect of previous safety alerts; and 3.) operating an early warning system.[339] In the wake of Vioxx, FDA asked the Institute of Medicine of the National Academies to convene a committee of experts to assess the current system for evaluating and ensuring post-market drug safety, and to recommend ways to improve "risk assessment, surveillance, and the safe use of drugs."[340]

## PDUFA's Effects on FDA's Post-market Drug Safety Monitoring

### *Office of Drug Safety*

Although adverse event monitoring is far from an ideal means of monitoring post-market drug safety, under funding cripples FDA's ability to carry out effectively even that function.[341] FDA receives 1,000 adverse drug event reports every day, for which, as of 2002, around 50 safety evaluators and epidemiologists were responsible for reviewing.[342] Moreover, the volume of the reports received only conveys part of the story – follow-up investigation is often required in order to determine whether a particular reported event is due to the patient's medication, the underlying disease, or an extraneous cause, such as diet or alcohol intake.[343]

The reason FDA lacks adequate resources for post-market drug safety monitoring is the same reason that it has received an influx of resources for new drug reviews in recent years – the user fee program. As noted earlier,

to ensure industry monies were used to hire new drug reviewers and not merely to substitute for government support of existing FDA staff, PDUFA stipulated that user fee funds could only be used: 1.) to support new drug review activities; and 2.) if FDA continued to devote enough appropriated monies per year to new drug reviews – at least as much as it had devoted to new drug reviews in 1992 (later revised to 1997), adjusted for inflation.[344]

To be sure, these stipulations ensured that industry money was used only for new drug reviews. However, the requirement that FDA continue to allocate appropriated funds for new drug reviews at levels equal to or greater than the year the law was passed "increased the agency's focus on the reviews even beyond what the drug industry had negotiated."[345] A report by the GAO in 2002 found that in the years following enactment of PDUFA, congressional appropriations fell short of covering FDA's pay roll costs.[346] Specifically, FDA paid about $250 million in mandatory federal pay raises between fiscal years 1994 and 2001, for which it did not receive appropriations increases.[347] Accordingly, in order to meet PDUFA's required funding trigger, "FDA reduced the staffing levels for non-PDUFA activities each year, leaving the agency fewer resources to perform its other responsibilities."[348]

*In 1992, the year PDUFA was passed, FDA's CDER spent 53 percent of its budget on new drug reviews. By 2002, that proportion had increased by nearly half – 74 percent of CDER's $282 million budget went toward new drug reviews. In contrast, the Office of Drug Safety comprised less than six percent of CDER's 2002 budget.*

The Office of Drug Safety suffered as the result of the funding squeezes caused by the twin forces of lagging congressional appropriations and the PDUFA trigger. In 1992, the year PDUFA was passed, FDA's CDER spent 53 percent of its budget on new drug reviews, with the remainder supporting survey programs, laboratories and other efforts that contributed to ensuring post-market drug safety.[349] By 2002, that proportion had increased by nearly half – 74 percent of CDER's $282 million budget went toward new drug reviews.[350] In contrast, the Office of Drug Safety comprised less than six percent of CDER's 2002 budget.[351] As the result of cuts necessary to keep appropriated funds for new drug review high enough to qualify for user fees, in the mid-1990s FDA was forced to forgo collaboration with academic groups that complemented its adverse event reporting system.[352] Accordingly, the agency has become increasingly reliant on the drug industry for tests of side effects.[353]

### *Division of Drug Marketing, Advertising and Communications*

Another office within CDER has suffered as resources have been increasingly devoted to new drug approvals. FDA's drug-marketing enforcement office (DDMAC) plays an important, though less direct, role in drug safety. The period immediately after a drug first goes onto the market is critical for at least two reasons – as larger populations are first being exposed to the drug, which was previously tested only in pre-market clinical trials, the risk of manifestation of previously undetected side effects is at its highest.[354] This period of heightened safety risk coincides with the time during which the drug's sponsor will be most invested in promoting and marketing its product, which, in turn, maximizes the drug's exposure. Direct-to-consumer advertising, particularly that which emphasizes benefits and downplays risks, leads patients to demand (and, often, receive) these "least time-tested" drugs immediately upon initial FDA approval.[355] For example, Merck's advertising campaign for Vioxx may have increased demand for the drug among persons who had no particular need for the drug's reduced risk of GI complications, which was its only benefit over older NSAIDS such as ibuprofen.[356]

Collectively, pharmaceutical companies spend $3.8 billion per year in direct-to-consumer marketing of prescription drugs – a sum that "even exceeds what one of the very largest marketers, Unilever, spends annually on global campaigns for all its brands, including Dove, Knorr, Lipton, Lux, Pond's, Slim-Fast and Wish-Bone."[357] The task of reviewing the more than 30,000 pieces of promotional material generated every year by the industry's massive expenditures falls on 40 FDA employees.[358] FDA's DDMAC budget in 2002 was $3 million – one percent of CDER's total budget for that fiscal year.[359]

### *Other 'Side Effects' of PDUFA*

The ramifications of PDUFA's funding restrictions and requirements extend beyond FDA's ability to monitor post-market drug safety. Between 1992 and 2001, to cover the costs of mandatory federal pay raises while directing enough money to the new drug review process to maintain its ability to spend user fees, FDA shifted personnel resources to drug and biologic review activities and away from other activities. Specifically, in 2001, about 1,000 more full-time equivalents (FTEs) were allotted to drug and biologic review activities and 1,000 fewer FTEs to other FDA programs that "ensure drug safety, approve new medical devices such as heart valves and pacemakers, and monitor devices once on the market."[360]

As noted earlier, the statutory funding constraints are not the only conditions FDA must meet to retain the user fees – the performance goals memorialized in letters to congress are part and parcel of what the industry bargained for in agreeing to the user fee program.[361] The goals established for the renewal of PDUFA in the FDAMA (PDUFA II) included accelerated time frames for completion of application reviews as well as commitments intended to further the statutory objective of FDA working with drug sponsors to "reach[ ] agreement on the design and size of clinical trials."[362]

The GAO's investigation found that the PDUFA II performance goals increased FDA's workload, particularly those related to the requirement that FDA work with drug sponsors early in the drug development process.[363] Under the goals, FDA must act within specified time frames on matters pertaining to formal meetings with drug sponsors: review and respond to a meeting request within 14 days; schedule major meetings within either 60 or 75 days, depending on the phase of development for the drug involved; and prepare meeting minutes within 30 days of meetings.[364] The drain on resources imposed by such requirements becomes clear in light of the time requirements for formal meetings. From preparation through completion of minutes, each meeting can demand between 135 to 545 hours from the 17 FDA reviewers typically involved.[365]

The GAO also found that during the 3-year period following enactment of PDUFA II, FDA's attrition rates for drug reviewers were higher than rates for comparable occupations at other public health agencies.[366] FDA officials attributed the high turnover, in part, to the higher salaries that experienced FDA reviewers can earn in the private sector.[367] Finally, those employees who do remain are likely to fall below FDA's recommended levels of training and professional development in order to devote sufficient time to "ensure that the agency meets PDUFA goals."[368]

## *PDUFA III: A Step in the Right Direction, But Problems Remain*

Congress reauthorized the prescription drug user fee program for a second time in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PDUFA III).[369] Following the string of safety-based drug withdrawals between 1997 and 2001, Congress added "strengthening and improving the review and monitoring of drug safety" to FDA's charge under PDUFA III.[370] The stipulations that user fees could be used only: 1.) for "the process for the review of human drug applications"; and 2.) provided appropriations for "the process of the review of human drug applications" never fell below 1997 levels (adjusted for inflation) remained.[371] However, Congress expanded the definition of "process for the review of human drug applications" to include "collecting, developing, and reviewing safety information on the drugs, including adverse event reports, during a period of time after approval of applications on such supplements, not to exceed three years."[372] Accordingly, in theory, user fees could now be used for drug safety activities, and appropriations for those activities could be included in the "trigger" amount necessary to allow FDA to spend the fees.

PhRMA agreed with FDA in joint recommendations to Congress for PDUFA reauthorization that FDA should employ user fees "to fund a new risk management system for newly approved drugs."[373] The new system is a voluntary program, under which "drug sponsors may develop, and FDA will review, risk management plans for products while the agency reviews the sponsor's NDA . . . ."[374] Additionally, for "products that require risk management beyond standard labeling," FDA may use user fees for postmarket surveillance activities for three years."[375]

Although a step in the right direction, these nominal improvements to PDUFA will not solve the problems caused by its former incarnations. FDA's 2003 five-year

plan for PDUFA III shows the agency will dedicate less than eight percent of user fee revenues to post-market risk management.[376] Although FDA's post-Vioxx 2006 budget "proposes to dedicate $6.5 million more" than in fiscal year 2005 to the Office of Drug Safety,[377] that office's $33.4 million budget still represents just seven percent of CDER's total budget.[378]

The real problem posed by PDUFA was not a mere definitional constraint but its overall emphasis on speeding new drug reviews at the expense of all other activities. That emphasis remains. The performance goals under PDUFA III are the same as under PDUFA II.[379] Without significant increases in total funding, FDA will be unable to translate the easing of legal constraints on drug safety spending into real increases in resources for post-market drug safety monitoring.

## Conclusion

History's examples of the results of an unregulated market in drugs demonstrate that FDA is a critical consumer protection agency. Chafing at the agency's market interference, drug companies and conservative interests complained for years that FDA was taking too long to review new drugs. Arguments that ingrained biases, not inadequate resources, were to blame for the delays were proven wrong when the influx of resources from PDUFA indeed sped new drug approvals. A string of safety-based drug withdrawals in the late 1990s served as a reminder that although society has progressed beyond the days of the patent medicines and their outlandish cure-all claims, the public still needs an independent regulator to protect it from the dangers posed by directly-ingested chemical compounds.

Increased exposure to new drugs whose side effects are not fully known requires increased post-market drug safety monitoring to quickly spot previously undetected dangerous side effects. However, rather than providing a commensurate increase in resources for drug safety monitoring, PDUFA focused exclusively on moving drugs to market more quickly, and, worse, "sapped resources from other very needed areas."[380] Just as private markets are unable to weed out unsafe drugs without thalidomide-scale tragedies, few incentives exist for drug companies to actively seek out safety risks posed by their products once they are on the market, particularly if tort reform proposals eliminate the specter of product liability and its incentives for self-regulation. Public sector intervention is necessary to keep consumers safe from unreasonable risks posed by drugs, including those that emerge only after a drug is approved and on the market. Despite corrections to the legislative language that caused the technical inability to allocate sufficient funds to post-market risk management activities, PDUFA's emphasis remains on new drug approvals.

To better ensure that the benefits that accompany faster access to new drugs are not outweighed by risks that may become apparent only after approval, the following reforms deserve consideration. If Congress elects to retain the current system of industry user fees,[381] it must eliminate the performance goals for new drug reviews so that FDA can translate into action the legal ability provided it under PDUFA III to allocate money to post-market drug safety activities.[382] Further, Congress should authorize FDA to impose substantial civil monetary penalties against companies that fail to honor commitments to conduct post-market drug safety studies.[383] Additionally, it should provide FDA with the legal authority to demand, not negotiate, revised product labeling when new safety risks emerge after a drug is on the market.[384] Finally, to aid FDA in determining whether new warnings achieve their intended effect, or whether drug withdrawal is necessary to protect the public, Congress should expand FDA's post-market safety mandate to include surveillance of the most important known and expected risks.[385]

Amid the various proposals that have been – and will be – made for improving FDA's drug safety monitoring, one thing is clear. Public funding is necessary to supply FDA with sufficient resources to perform the truly public function of quickly identifying previously undetected drug side effects and, when necessary, requiring that dangerous drugs be pulled from the market. FDA's history is characterized by examples of Congress acting to increase FDA's authority after drug safety tragedies. Inadequate funding has consistently hobbled the agency's ability to fulfill the functions envisioned for it in legislation. Congress should follow history's example and respond to Vioxx, perhaps the "single biggest drug catastrophe in U.S. history," by strengthening FDA – this time by providing sustained increases in funding for drug safety.

## About the Authors

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## *Appendix: Safety-Based Withdrawals of FDA Approved Drugs (1997-2001)*

| Drug Name | Year Withdrawn | Use | Risks | Year Approved |
|---|---|---|---|---|
| Baycol (cerivastatin) | 2001 | Cholesterol drug | Rhabdomyolysis, severe damage to muscle that is sometimes fatal | 1997 |
| Raplon (rapacuronium bromide) | 2001 | Injectable anesthesia administered as a relaxant for breathing tube placement and surgery | Bronchospasm, an inability to breathe normally that can lead to permanent injury or death | 1999 |
| Lotronex (alosetron) | 2000 | Treatment for irritable bowel syndrome in women | Intestinal damage resulting from reduced blood flow to the intestine (ischemic colitis) and severely obstructed or ruptured bowels (complications of severe constipation) | 2000 |
| Propulsid (cisapride) | 2000 | Treatment for nighttime heartburn | Fatal heart rhythm abnormalities | 1993 |
| Phenylpropanolamine | 2000 | Decongestant used in many prescription and over-the-counter cough and cold medications | Hemorrhagic stroke (bleeding in the brain) | **[387] |
| Rezulin (troglitazone) | 2000 | Treatment for type 2 diabetes | Severe liver toxicity | 1997 |
| Hismanal (astemizole) | 1999 | Antihistamine | Fatal heart rhythm abnormalities when used with other drugs or at too high a dose | 1988 |
| Raxar (grepafloxacin) | 1999 | Antibiotic | Risk of fatal heart rhythm abnormalities | 1997 |
| Posicor (mibefradil) | 1998 | Treatment for high blood pressure and chronic stable angina | Dangerous interactions with other drugs | 1997 |
| Duract (bromfenac) | 1998 | Pain reliever | Severe liver damage | 1997 |
| Seldane (terfenadine) and Seldane-D | 1998 | Antihistamine | Fatal heart rhythm abnormalities | 1985 |
| Pondimin (fenfluramine) | 1997 | Treatment for obesity | Heart valve abnormalities | 1973 |
| Redux (dexfenfluramine) | 1997 | Treatment for obesity | Heart valve abnormalities | 1996 |

Source: U.S. Food and Drug Administration, FDA Consumer Magazine (Jan.-Feb. 2002).

## Notes

[1] U.S. Food and Drug Administration, Vioxx (rofecoxib) Questions and Answers (Sept. 30, 2004), ¶¶ 2, 9, available online at: http://www.fda.gov/cder/drug/infopage/vioxx/vioxxQA.htm (last visited Oct. 18, 2005) [hereinafter, FDA, Vioxx Q&A].

[2] *See*, *e.g.*, Andrew Pollack, *New Scrutiny of Drugs in Vioxx's Family*, N.Y. Times, Oct. 4, 2004, § C.

[3] *See e.g.*, Gardiner Harris and Alex Berenson, *10 Voters on Panel Backing Pain Pills Had Industry Ties*, N.Y. Times, Feb. 25, 2005, § A (noting that Vioxx and other drugs in its class "have never been proved in clinical trials to cure pain any better" than existing drugs); Andrew Pollack, *Merck and Vioxx: The Patients; Doctors Tell Vioxx Users That Alternative Are Available*, N.Y. Times, Oct. 1, 2004, § C (stating that "Vioxx provides no better pain relief than many older and far less expensive anti-inflammatory drugs). However, "[s]ome patients find that one drug works better for them, for reasons that doctors cannot necessarily determine. 'Many people who took Vioxx were those for whom other medications had not worked.'" Mary Duenwald, *For Pain Management, Doctors Prescribe Caution*, N.Y. Times, Feb. 20, 2005, § 1 (quoting Dr. Sudhir Diwan, director of the division of pain medicine at New York-Presbyterian Hospital).

[4] FDA, Vioxx Q&A, *supra* note 1, ¶10.

[5] Pollack, *supra* note 2.

[6] *Id.*

[7] *FDA, Merck and Vioxx: Putting Safety First?: Hearing Before the Senate Comm. on Fin.,* 108th Cong. 2 (2004) (statement of Gurkipal Singh, M.D., Adjunct Clinical Department of Medicine, Stanford University School of Medicine) [hereinafter, *FDA, Merck and Vioxx Hearings* (Dr. Gurkipal Singh)].

[8] *Id.*

[9] Pollack, *supra* note 2.

[10] *Id.*

[11] *Id.*

[12] *FDA, Merck and Vioxx: Putting Safety First?: Hearing Before the Senate Comm. on Fin.,* 108th Cong. 2 (2004) (statement of Bruce Psaty, M.D., Ph.D., Professor, Medicine, Epidemiology and Health Services and Co-director, Cardiovascular Health Research Unit, University of Washington) [hereinafter, *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty)].

[13] Pollack, *supra* note 2.

[14] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 2.

[15] *See* Merck & Co., Inc., Press Release, Merck Announces Voluntary Worldwide Withdrawal of VIOXX (Sept. 30, 2004), available online at: http://www.vioxx.com/rofecoxib/vioxx/consumer/press_release_09302004.jsp (last visited Sept. 9, 2005) [hereinafter, Merck Press Release: Vioxx Withdrawal].

[16] *Id.* APPROVe stood for "Adenomatous Polyp Prevention on VIOXX." *Id. See also*, Eric J. Topol, *Good Riddance to a Bad Drug*, N.Y. Times, Oct. 2, 2004, § A.

[17] Alex Berenson, *et al.*, *Dangerous Data – Retracing a Medical Trail; Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. Times, Nov. 14, 2004, § 1.

[18] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 3.

[19] *Id.* (citing M. L. Villalba, *FDA Medical Officer Review of Vioxx (rofecoxib), NDA 21-042 (capsules) and NDA 21-052 (oral solution)*, 105).

[20] *Id.* (citing M. L. Villalba, *FDA Medical Officer Review of Vioxx (rofecoxib), NDA 21-042 (capsules) and NDA 21-052 (oral solution)*, 105).

[21] *Id.*

[22] *Id.* at 3-4.

[23] *Id.* at 4.

[24] *FDA, Merck and Vioxx: Putting Safety First?: Hearing Before the Senate Comm. on Fin.,* 108th Cong. 1 (2004) (statement of Sandra Kweder, M.D., Deputy Director, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration) [hereinafter, *FDA, Merck and Vioxx Hearings* (Dr. Sandra Kweder)].

[25] *Id.*

[26] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 4.

[27] *Id.*

[28] *Id.*

[29] *Id.*

[30] Letter from Thomas W. Abrams, R.Ph., MBA, Director, Division of Drug Marketing, Advertising and Communications, U.S. Food and Drug Administration, to Raymond V. Gilmartin, President and CEO, Merck & Co., Inc. 1 (Sept. 17, 2001) (available online at: http://www.fda.gov/cder/warn/2001/9456.pdf (last visited Sept. 14, 2005)).

[31] *Id.*

[32] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 6.

[33] Memorandum from Rep. Henry Waxman to Democratic Members of the Government Reform Committee re: *The Marketing of Vioxx to Physicians*, 27 (May 5, 2005), *available at* http://www.democrats.reform.house.gov/story.asp?ID=848&Issue=Prescription+Drugs (last visited Oct. 3, 2005) [hereinafter, Government Reform Committee Vioxx Memo].

[34] *See, e.g.* Philip J. Hilts, Protecting America's Health, The FDA, Business, and One Hundred Years of Regulation, 234 (Alfred A. Knopf, New York 2003) [hereinafter, Hilts, Protecting America's Health] (stating that "labels are not written by the FDA; they too are negotiated with the company); *Drug Safety on Trial*, 434 Nature 545 (2005) (arguing that FDA needs authority to "dictate – rather than negotiate with drug-makers, as the FDA currently does – that beefed-up warning labels are used when evidence of new risks emerges"); Government Reform Committee Vioxx Memo, 26 (stating that "[u]nder the federal Food, Drug and Cosmetic Act, FDA and manufacturers must agree on label changes.").

[35] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 6; *See also* FDA, Vioxx Q&A, *supra* note 1 at ¶9. The VIGOR study was discussed at a February 2001 Arthritis Advisory Committee. *Id.* For a timeline of events related to the Vioxx withdrawal, *see Vioxx Timeline: 1998 – 2005*, TheStreet.com, available at: http://www.thestreet.com/pf/stocks/biotech/10239081.html (last visited Oct. 3, 2005).

[36] Government Reform Committee Vioxx Memo, *supra* note 33 at 26. The company's former head research scientist, Edward Scolnick, dismissed one such proposal as "ugly." John Curran, *Merck Exec Testifies About Battle over Vioxx Warning Label*, Associated Press, Sept. 26, 2005, *available at*: http://www.washingtonpost.com/wp-dyn/content/article/2005/09/26/AR2005092601208.html (last visited Oct. 9, 2005). For a discussion of issues that Merck and FDA disagreed on during the Vioxx label-change negotiations other than whether VIGOR information would be included in the "warnings" or the "precautions" section of the Vioxx label, *see* Government Reform Committee Vioxx Memo, *supra* note 33 at 26-28.

[37] Government Reform Committee Vioxx Memo, *supra* note 33 at 27.

[38] *Id.*; Curran, *supra* note 36. While negotiating with FDA to keep the information out of the "warnings" section, an internal e-mail from Edward Scolnick (Merck's former head research scientist) told colleagues, "To all: If you get this label, it will be an Al Michaels quote: Do you believe in miracles?" *Id.*

[39] FDA, Vioxx Q&A, *supra* note 1 at ¶9, Government Reform Committee Vioxx Memo, *supra* note 33 at 28.

[40] Curran, *supra* note 36.

[41] Eric J. Topol, *Failing the Public Health – Rofecoxib, Merck, and the FDA*, 351 N. Engl. J. Med. 1707, 1708 (Oct. 21, 2004) [hereinafter, Topol, *Failing the Public Health*].

[42] Barnaby J. Feder, *Lawyers Organizing for Mass Suits over Vioxx*, N.Y. Times (November 5, 2004), § C.

[43] *The Experts' Verdict on Painkillers*, N.Y. Times (February 19, 2005), § A.

[44] Marc Kaufman, *Merck CEO Resigns as Drug Probe Continues*, Wash. Post, May 6, 2005 at A1; *See also* Government Reform Committee Vioxx Memo, *supra* note 33 at 17.

[45] *Id.*

[46] Donna Young, *Hearing Focuses on Vioxx Sales Maneuvers: Merck, FDA Discuss Potential Vioxx Return*, ASHP News, May 6, 2005, *available at* http://www.ashp.org/news/ShowArticle.cfm?id=10835 (last visited Oct. 3, 2005); *See*

*also* Government Reform Committee Vioxx Memo, *supra* note 33 at 17.

[47] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 6.

[48] *Id.* at 2.

[49] *FDA, Merck and Vioxx: Putting Safety First?: Hearing Before the Senate Comm. on Fin.,* 108th Cong. 2 (2004) (statement of David J. Graham, M.D., M.P.H., Associate Director for Science and Medicine, Office of Drug Safety, U.S. Food and Drug Administration [hereinafter *FDA, Merck and Vioxx Hearings* (Dr. David Graham)]).

[50] *Id.* at 3; *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 6; Gardiner Harris, *Regulation Redefined: The F.D.A. Shifts Focus; At F.D.A., Strong Drug Ties and Less Monitoring*, N.Y. Times, Dec. 6, 2004, § A [hereinafter, Harris, *Regulation Redefined*].

[51] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 6.

[52] *FDA, Merck and Vioxx Hearings* (David Graham), *supra* note 49 at 3.

[53] *Id.* The 20th International Conference on Pharmacoepidemiology & Therapeutic Risk Management was held in Bordeaux, France from August 22-25, 2004. *See* http://www.pharmacoepi.org/meetings/20thconf/index.cfm (last visited Oct. 11, 2005).

[54] *FDA, Merck and Vioxx Hearings* (Dr. David Graham), *supra* note 49 at 3.

[55] U.S. Food and Drug Administration, News Release, *FDA Statement on Vioxx and Recent Allegations and the Agency's Continued Commitment to Sound Science and Peer Review*, Nov. 17, 2004, *available at*: http://www.fda.gov/bbs/topics/news/2004/NEW01136.html (last visited Oct. 11, 2005); *See also FDA, Merck and Vioxx Hearings* (Dr. Sandra Kweder), *supra* note 24 at 4-5 .

[56] Merck Press Release: Vioxx Withdrawal, *supra* note 15.

[57] *FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 6; U.S. Food and Drug Administration, FDA Public Health Advisory: Safety of Vioxx (Sept. 30, 2004), available online at: http://www.fda.gov/cder/drug/infopage/vioxx/PHA_vioxx.htm (last visited Sept. 15, 2005). Although Merck communicated the recommendation of the Data Safety Monitoring Board (DSMB) to FDA, *see id.*, it did not include the DSMB's recommendation in its press release concerning the voluntary withdrawal. Merck Press Release: Vioxx Withdrawal, *supra* note 15.

[58] Annual sales of Vioxx in 2003 reached $2.5 billion. Barry Meier, *Merck and Vioxx: The Clinical Tests; For Merck, Defense of a Drug Crumbles at a Difficult Time*, N.Y. Times, Oct. 1, 2004, § C; *See also* Topol, *Failing the Public Health*, *supra* note 41.

[59] Merck Press Release: Vioxx Withdrawal, *supra* note 15.

[60] *FDA, Merck and Vioxx Hearings* (Dr. David Graham), *supra* note 49 at 1.

[61] *Id.* at 2.

[62] *See, e.g.,* FDA, Vioxx Q&A, *supra* note 1 at ¶ 10.

[63] *See, e.g.,* Berenson, *et al.*, *supra* note 17.

[64] *See, e.g.*, Harris, *Regulation Redefined, supra* note 50; Gardiner Harris, *Drug Safety Reviewer Says FDA Delayed Vioxx Study*, N.Y. Times (November 4, 2004), § A.

[65] *FDA, Merck and Vioxx Hearings* (Dr. David Graham), *supra* note 49 at 4.

[66] Harris, *Regulation Redefined, supra* note 50.

[67] U.S. Food and Drug Administration, Office of Womens Health, *FDA Milestones in Women's Health*: *Looking Back as We Move into the New Millennium*, available online at: http://www.fda.gov/womens/milesbro.html [hereinafter, FDA, Milestones in Women's Health]; *See also* Fran Hawthorne, Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat, 24 (John J. Wiley & Sons, Hoboken, New Jersey 2005).

[68] Meat and poultry are regulated by the U.S. Department of Agriculture. FDA, Backgrounder: *Food Safety: A Team Approach* (September 24, 1998), available online at: http://www.cfsan.fda.gov/~lrd/foodteam.html. The Environmental Protection Agency "[d]etermines safety of new pesticides, sets tolerance levels for pesticide residues in foods, and publishes directions on safe use of pesticides." *Id.*

[69] FDA, Milestones in Women's Health, *supra* note 67.

[70] Hawthorne, *supra* note 67 at x.

[71] Mitchell Okun, Fair Play in the Marketplace: The First Battle for Pure Food and Drugs, ix (Northern Illinois University Press, Dekalb, Illinois 1986).

[72] Hilts, Protecting America's Health, *supra* note 34 at 22.

[73] James Harvey Young, Pure Food: Securing the Federal Food and Drugs Act of 1906, 31 (Princeton University Press, Princeton, New Jersey 1989) [hereinafter, Young, Pure Food].

[74] *Id.* at 34.

[75] Hilts, Protecting America's Health, *supra* note 34 at 23.

[76] *Id.* at 24.

[77] James Harvey Young, The Toadstool Millionaires: A Social History of Patent Medicines in America before Federal Regulation, 40 (Princeton University Press, Princeton, New Jersey 1961) [hereinafter, Young, The Toadstool Millionaires].

[78] Hilts, Protecting America's Health, *supra* note 34 at 24.

[79] Young, The Toadstool Millionaires, *supra* note 77 at 39.

[80] Hilts, Protecting America's Health, *supra* note 34 at 25.

[81] Young, The Toadstool Millionaires, *supra* note 77 at 60.

[82] Hilts, Protecting America's Health, *supra* note 34 at 25.

[83] Young, The Toadstool Millionaires, *supra* note 77 at 61-62.

[84] *Id.* at 65.

[85] *See id.* at 221-22.

[86] *Id.* at 68-69.

[87] Young, Pure Food, *supra* note 73 at ix. Detailed accounts of the events preceding the Food and Drugs Act of 1906 are contained in Young, Pure Food, Okun, *supra* note 71, and Lorine Swainston Goodwin, The Pure Food, Drink, and Drug Crusaders, 1879-1914 (McFarland & Co., Inc., Jefferson, North Carolina 1999).

[88] Hilts, Protecting America's Health, *supra* note 34 at 17.

[89] Young, Pure Food, *supra* note 73 at 102.

[90] Hilts, Protecting America's Health, *supra* note 34 at 36.

[91] *Id.* at 35-36.

[92] *Id.* at 39.

[93] Young, Pure Food, *supra* note 73 at 152-56.

[94] Hilts, Protecting America's Health, *supra* note 34 at 40.

[95] *Id.* at 39-40.

[96] Young, Pure Food, *supra* note 73 at 157.

[97] *Id.* at 201-03.

[98] Hilts, Protecting America's Health, *supra* note 34 at 49; Young, Pure Food, *supra* note 73 at 204.

[99] Hilts, Protecting America's Health, *supra* note 34 at 51. Upton Sinclair was an avowed socialist, and hoped, through *The Jungle*, to advance his political agenda through an expose of "wage slavery", a fact that contributed to President Roosevelt's skepticism. Writing to Sinclair about *The Jungle*, Roosevelt stated "Personally I think that one of the chief early effects of such attempt to put socialism . . . into practice, would be the elimination by starvation, and the diseases, moral and physical, attendant upon starvation, of that same portion of the community on whose behalf socialism would be invoked." Letter from Theodore Roosevelt to Upton Sinclair, March 15, 1906, *reprinted in* Louis Auchincloss, ed., Theodore Roosevelt: Letters and Speeches (Literary Classics of the United States, Inc., New York 2004), 452. Nonetheless, Roosevelt concluded his letter by stating that "all this has nothing to do with the fact that the specific evils you point out shall, if their existence be proved, and if I have power, be eradicated." *Id.* at 453.

[100] Hilts, Protecting America's Health, *supra* note 34 at 53.

[101] *See id.* at 53.

[102] *Id.* at 53.

[103] *Id.* at 54.

[104] *Id.* at 55.

[105] Edmund Morris, Theodore Rex (Random House, New York 2001), 448 (quoting Ray Stannard Baker in *The Railroad Rate: A Study in Commercial Autocracy*, McClure's, November 1905). However, one historian has noted that the Food and Drugs Act of 1906 "resembled other Progressive legislation in its 'appearance of radical reform without the substance.'" Young, Pure Food, 290 (quoting Robert M. Crunden, Ministers of Reform: the Progressives' Achievement in American Civilization, 1889-1920 (Basic Books, New York 1982)).

[106] Hilts, Protecting America's Health, *supra* note 34 at 74.

[107] *Id.*

[108] *Id.* at 75.

[109] James Harvey Young, The Medical Messiahs: A Social History of Health Quackery in Twentieth Century America, 54 (Princeton University Press, Princeton, New Jersey 1967) [hereinafter, Young, The Medical Messiahs].

[110] Hilts, Protecting America's Health, *supra* note 34 at 84-85. Lash lure mascara was among the exhibits in an FDA's so called "Chamber of Horrors," a series of posters with bottles, labels, advertisements and death certificates attached, each depicting a "hazard to life or limb which the FDA could prevent only with difficulty or not at all under existing law." Young, The Medical Messiahs, *supra* note 109 at 169. Originally devised to bolster Commissioner Campbell's testimony before the Senate concerning continuing dangers of self-medication, the exhibit attracted significant public attention. *Id.* at 169-70.

[111] Hilts, Protecting America's Health, *supra* note 34 at 75.

[112] *Id.* at 77 (citing Michael Namorato, ed., The Diary of Rexford G. Tugwell: The New Deal, 1932-1935, 85 (Greenwood Press, New York 1992)). Tugwell was "frank to say he believed in a planned economy" and had spent two months in Russia. Young, The Medical Messiahs, *supra* note 109 at 160. He had openly questioned whether the majority of U.S. sales effort and expense served "any good social purpose." *Id.* Seizing upon Tugwell's economic equity concerns, the proprietary medicine industry would, when draft legislation to reform the Food and Drugs Act of 1906 was circulated, issue dire predictions that the so-called Tugwell bill would, among other things "sovietize" U.S. drugstores. *Id.* at 167.

[113] *Id.* at 158-59.

[114] *Id.* at 159.

[115] *Id.* at 160.

[116] Hilts, Protecting America's Health, *supra* note 34 at 79.

[117] *Id.*

[118] *Id.* at 89.

[119] *Id.*

[120] *Id.*

[121] Young, The Medical Messiahs, *supra* note 109 at 184.

[122] Hilts, Protecting America's Health, *supra* note 34 at 92. As Hilts notes, not counted in that statistic was the Massengill Company's chief chemist, Harold C. Watkins, who committed suicide after the effects of his chosen solvent became apparent.

[123] *Id.* at 92-93.

[124] Young, The Medical Messiahs, *supra* note 109 at 188 (citing Cong. Rec. (75 Cong., 3 ses.), 8731-38, 9087-9101, 9616).

[125] *See* Hilts, Protecting America's Health, *supra* note 34 at 129-35.

[126] *Id.* at 140.

[127] *Id.* at 141.

[128] *Id.* at 140.

[129] *Id.*

[130] *Id.* at 142.

[131] *See id.* at 143, 154.

[132] Young, The Medical Messiahs, *supra* note 109 at 415; *See also* FDA, *Thalidomide: Important Patient Information*, DHHS Publication No.(FDA) 96-3222 (Sept. 11, 1997), *available at* http://www.fda.gov/cder/news/thalidomide.htm (last visited Oct. 18, 2005).

[133] *See* HILTS, PROTECTING AMERICA'S HEALTH, *supra* note 34 at 152.

[134] *See id.*

[135] *Id.*

[136] YOUNG, THE MEDICAL MESSIAHS, *supra* note 109 at 415.

[137] *Id.* at 416-17.

[138] *Id.* at 417.

[139] *Id.* at 416. In its early days, thalidomide had promised to be a safer sedative than most because it did not, unlike many of its counterparts, cause death when taken in large doses. *Id.* at 415.

[140] *Id.* at 416.

[141] HILTS, PROTECTING AMERICA'S HEALTH, *supra* note 34 at 158.

[142] YOUNG, THE MEDICAL MESSIAHS, *supra* note 109 at 417.

[143] *Id.*

[144] *Id.* at 417-18.

[145] *Id.* at 418.

[146] Jeffrey E. Shuren, *The Modern Regulatory Administrative State: A Response to Changing Circumstances*, 38 HARV. J. ON LEGIS. 291, 302 (2001) (citing 21 U.S.C. § 355(d)).

[147] HILTS, PROTECTING AMERICA'S HEALTH, *supra* note 34 at 164.

[148] Shuren, *supra* note 146 at 291, 302.

[149] HILTS, PROTECTING AMERICA'S HEALTH, *supra* note 34 at 164.

[150] Shuren, *supra* note 146 at 302 (citing 21 U.S.C. § 321).

[151] HILTS, PROTECTING AMERICA'S HEALTH, *supra* note 34 at 343.

[152] HILTS, PROTECTING AMERICA'S HEALTH, *supra* note 34 at 308.

[153] *See e.g.*, EDGAR K. BROWNING & MARK A. ZUPAN, MICROECONOMICS: THEORY & APPLICATIONS, 7th ed. (John Wiley & Sons, Inc. 2002), 397.

[154] C. Frederick Beckner, III, *The FDA's War on Drugs*, 82 GEO. L.J. 529, 530 (1993) (citing Henry Beales *et al.*, *The Efficient Regulation of Consumer Information*, 24 J.L. & ECON. 491, 492 (1981)).

[155] YOUNG, THE MEDICAL MESSIAHS, *supra* note 109 at 184 (detailing that the chemist who had decided upon diethylene glycol had been "unaware of reports describing the compound's toxicity" and had "tested his new concoction for appearance, fragrance and flavor—but not for safety.")

[156] Elizabeth M. Rutherford, *The FDA and "Privatization" – The Drug Approval Process*, 50 FOOD & DRUG L.J. 203, 212 (1995) (citing 48 Fed. Reg. 26,720, 26723 (1983)).

[157] *Id.* (citing 21 C.F.R. § 312.23 (1995)).

[158] *Id.* at 213 (citing 21 C.F.R. § 312.1 *et seq*. (1995)). The Institutional Review Boards in the institutions where the drug will be tested must also approve the proposed clinical studies. *Id.* (citing 21 C.F.R. § 312.66 (1995)).

[159] *Id.* (citing Pharmaceutical Research & Mfrs. of America, Drug Development and Regulatory Issues, 3 (1994)).

[160] *Id.*

[161] *Id.*

[162] *Id.* (citing Mary M. Dunbar, *Shaking Up the Status Quo: How AIDS Activists Have Challenged Drug Development and Approval Procedures*, 46 FOOD DRUG COSM. L.J. 673, 682 (1991)).

[163] *Id.* (citing 21 C.F.R. § 314.1 *et seq*. (1995)).

[164] Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 458 (2000) (citing 21 C.F.R. § 312.21).

[165] *Id.* (citing Peter Huber, *Safety and the Second Best*: *The Hazards of Public Risk Management in the Courts*, 85 COLUM. L. REV. 277, 304-05 (1985)).

[166] *See*, *e.g.*, Mark B. McClellan, *Analyzing the Laws, Regulations and Policies Affecting FDA-Regulated Products*, 58 FOOD & DRUG L.J. 191, 197(2003) (stating that "even with the best available data, drugs are sometimes found to have adverse effects that could not have been predicted or uncovered in any feasible clinical trial.").

[167] Noah, *supra* note 164 at 458.

[168] David A. Kessler, *Introducing MedWatch: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems*, 269 JAMA 2765 (1993) [hereinafter, Kessler, *Introducing MedWatch*].

[169] Noah, *supra* note 164 at 458-59.

[170] *See id.* at 459 (citing Alistair J.J. Wood *et al.*, *Making Medicines Safer – The Need for an Independent Drug Safety Board*, 339 New Eng. J. Med. 1851, 1852 (1998)).

[171] *See* Thomas J. Moore, *et al.*, *Time to Act on Drug Safety*, 279 JAMA 1571 (1998) (citing U.S. General Accounting Office, GAO/PEMD-90-15, FDA Drug Review: Postapproval Risks, 1976-85 (1990)).

[172] Interview by Frontline with Raymond Woosley, M.D., Vice President for Health Sciences, University of Arizona (Oct. 25, 2002), available online at: http://www.pbs.org/wgbh/pages/frontline/shows/prescription/interviews/woosely.html (last visited 08/17/2005) [hereinafter Frontline Interview, Dr. Raymond Woosley].

[173] Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS and the Diet Drug Debacle*, 79 B.U. L. Rev. 93, 96 (1999).

[174] Young, The Medical Messiahs, *supra* note 109 at 270.

[175] W. M. Wardell, *Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison*, 14 Clinical Pharmacology & Therapeutics 773 (1973).

[176] Hilts, Protecting America's Health, *supra* note 34 at 190 (citing Wardell, *supra* note 175).

[177] *Id.* at 190-91 (citing Wardell, *supra* note 175).

[178] *Id.* at 192-93 (citing Sam Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. Pol. Econ. 1049 (1973)).

[179] FDA and Dr. Sidney Wolfe of the Public Citizen Health Research Group pointed out that Wardell's "drug lag" study measured mostly unimportant drugs and failed to account for drugs that were approved elsewhere but should not have been. *Id.* at 192. Peltzman's study failed to adequately account for the benefits associated with the pre-market review mandated by the Kefauver-Harris amendments. *Id. See also*, *e.g.*, Robert W. Hahn & John A. Hird, *The Costs and Benefits of Regulation: Review and Synthesis*, 8 Yale J. on Reg. 233, 276-77 (1991).

[180] *See* Letter from Elmer B. Staats, Comptroller General to the Honorable George E. Brown, Jr., Chairman, Subcommittee on Science, Research and Technology, Committee on Science and Technology, U.S. House of Representatives (May 28, 1980) (contained in U.S. Gen. Accounting Office, GAO/HRD-80-64, FDA Drug Approval: A Lengthy Approval Process that Delays the Availability of Important New Drugs (1980) (available online at http://archive.gao.gov/d46t13/112450.pdf) (last visited 09/02/2005) [hereinafter, GAO: FDA Drug Approval]).

[181] GAO: FDA Drug Approval, *supra* note 180 at 9, 11. The countries for which the GAO compared the length of new drug approvals were: Canada, Norway, Sweden, Switzerland, the United Kingdom and the United States. *Id.* at 11.

[182] GAO: FDA Drug Approval, *supra* note 180, cover page.

[183] *Id.* at 9.

[184] *Id.* at 27.

[185] *Id.* at 9, 11. The countries for which the GAO compared the length of new drug approvals were: Canada, Norway, Sweden, Switzerland, the United Kingdom and the United States. *Id.* at 17.

[186] Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1776-77 (1996).

[187] Hilts, Protecting America's Health, *supra* note 34 at 165 (noting that in enacting Kefauver-Harris amendments and "getting serious about science and testing to protect the public," Congress "did what it had often done before: it voted to give the agency new duties and responsibilities while failing to provide the money to allow the agency to carry them out").

[188] Margaret Gilhooley, *FDA and the Adaptation of Regulatory Models*, 49 St. Louis U. L.J. 131, 133 (2004).

[189] James Harvey Young, American Health Quackery, 256 (Princeton University Press, Princeton, New Jersey 1992) [hereinafter, Young, American Health Quackery]; Hawthorne, Inside the FDA, *supra* note 67 at 51.

[190] *See*, *e.g.*, Hawthorne, Inside the FDA, *supra* note 67 at 51.

[191] *See* Hilts, Protecting America's Health, *supra* note 34 at 7.

[192] Attention on the efforts of AIDS activists peaked on October 11, 1988 during a protest outside FDA headquarters in Rockville, Maryland. Demonstrators raised a black flag on the building's flagpole and hanged President Reagan and Commissioner Young in effigy. *See*, *e.g.*, Hawthorne, Inside the FDA, *supra* note 67 at 53-54.

[193] Young, American Health Quackery, *supra* note 189 at 271 (citing *Therapeutic Drugs for AIDS: Development, Testing, and Availability*: *Hearings before a Subcommittee of the Committee on Government Operations*, 100th Cong., 372-74, 411 (1988)).

[194] Salbu, *supra* note 173 at 103.

[195] Rutherford, *supra* note 156 at 219 (citing 21 C.F.R. § 312.34).

[196] *Id.* at 219.

[197] Young, American Health Quackery, *supra* note 189 at 270; 53 Fed. Reg. 41,516 (Oct. 21, 1988) (codified at 21 C.F.R. § 312.80-.88).

[198] Salbu, *supra* note 173 at 114.

[199] Rutherford, *supra* note 156 at 219. FDA approved AZT two years after the sponsor commenced clinical tests. *Id.*

[200] Salbu, *supra* note 173 at 115.

[201] Bruce N. Kuhlik, *Industry Funding of Improvements in the FDA's New Drug Approval Process: The Prescription Drug User Fee Act of 1992*, 47 Food & Drug L.J. 483, 487-88 (1992) (citing *Agriculture, Rural Development, Food and Drug Administration and Related Agencies Appropriations for 1993: Hearings Before a Subcomm. of the House Comm. on Appropriations*, 102d Cong., 2d Sess., pt. 6, at 5 (1992)).

[202] *Id.* at 483 (citing U.S. Gen. Accounting Office, Fees Not Charged for Processing Applications for New Drugs (1971)).

[203] *Id.* at 483-85 (explaining that, under Title V of the Independent Offices Appropriation Act of 1952, agencies may impose fees only for activities that directly benefit specific persons, not for activities that benefit the public at large and that the Department of Health, Education and Welfare (FDA's parent agency) initially took the position that the general public was the primary beneficiary of FDA's NDA review process).

[204] *Id.* at 485.

[205] *Id.* at 485-86.

[206] *Id.* at 485.

[207] *Id.* at 488 (citing *PMA Will Consider User Fees if Four Criteria Are Met*, PMA Newsletter, 2 (August 17, 1992)).

[208] *Id.*

[209] Merrill, *supra* note 186 at 1795-96, n. 131.

[210] Hilts, Protecting America's Health, *supra* note 34 at 279.

[211] Kuhlik, *supra* note 201 at 483; Pub. L. No. 102-571, 106 Stat. 4491 (1992).

[212] Merrill, *supra* note 186 (citing Section 105 of Pub. L. No. 102-571; 21 U.S.C. § 379g (1994)).

[213] David A. Kessler, *Remarks by the Commissioner of Food and Drugs*, 50 Food & Drug L.J. 327, 327-28 (1995).

[214] Anthony Lewis, *Abroad at Home; Reform or Wreck?*, N.Y. Times, January 27, 1995; *See also* Elizabeth C. Price, *Teaching the Elephant to Dance: Privatizing the FDA Review Process*, 51 Food & Drug L.J. 651, 652 (citing *In Defence of the FDA*, Lancet (October 14, 1995) at 981; *The Assault on Government by Republicans*, Progressive (Mar. 1995) at 8; Jeffrey P. Cohn, *The "Bully" Fights Back*, Government Executive (Apr. 1995)).

[215] *See* Joshua Wolf Shenk, *Warning: Cutting the FDA Could Be Hazardous to Your Health*, Washington Monthly (Jan. – Feb. 1996) at 17.

[216] Hilts, Protecting America's Health, *supra* note 34 at 297. A copy of the WLF advertisement is available at: http://tobaccodocuments.org/pm/2046936817.html (last visited Oct. 12, 2005).

[217] *See* Shenk, *supra* note 215 at 17.

[218] Price, *supra* note 214 at 654 (citing, *inter alia*, *Regulation of Pharmaceutical Innovation, 1973*: *Hearings Before the Subcomm. on Monopoly of the Senate Comm. on Small Business*, 93d Cong., 1st Sess. 9802, 9803-07 (1973) (remarks of economist Sam Peltzman)).

[219] Rutherford, *supra* note 156 at 214.

[220] Price, *supra* note 214 at 652.

[221] For a thorough account of the purported and actual facts surrounding six primary cases cited by the WLF (Interleukin, the CardioPump, Tacrine, the heart defribillator, the sensor pad and tissue plasminogen activator (TPA)), *see* Hilts, Protecting America's Health, *supra* note 34 at 297-308.

[222] Hilts, Protecting America's Health, *supra* note 34 at 297. A copy of the WLF advertisement is available at: http://tobaccodocuments.org/pm/2046936817.html (last visited Oct. 12, 2005). *See also* Alan M. Slobodin, WLF Legal Backgrounder, *The Real Problem with Health Care in America: While Dr. David Kessler's FDA Fiddles, Medical Approvals Lag and Americans Die*, 2 (Oct. 28, 1994).

[223] Susan Okie, *FDA Panel Refuses to Recommend Approval of Alzheimer's Drug*, Wash. Post, Mar. 16, 1991, A3.

[224] *Id.*

[225] *Id.*

[226] *Id.*

[227] Malcolm Gladwell, *FDA Urges Wider Access to Alzheimer's Treatment; Expanded Trials of Experimental Drug Tacrine Proposed*, Wash. Post, Mar. 23, 1991, A2.

[228] *Id.*; *See also* U.S. Food and Drug Administration, News Release 91-75, *Treatment IND for Alzheimer's Disease Drug* (Dec. 2, 1991), *available at* http://www.fda.gov/bbs/topics/ANSWERS/ANS00366.html (last visited Oct. 12, 2005).

[229] Gladwell, *supra* note 227 (quoting Alzheimer's Association President Edward Truschke stating that "[e]xpanded access to the trials and rapid data collection can only work in the favor of Alzheimer's patients around the country.").

[230] *Id.*

[231] *Id.*; 21 C.F.R. § 312.7(d)(2) (providing that drug sponsor may only charge for an investigational drug for treatment use provided specified conditions are met and FDA is notified); 21 C.F.R. § 312.7(d)(3) (prohibiting sponsors from "charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.).

[232] U.S. Food and Drug Administration, News Release P93-37 (Sept. 9, 1993), *available at* http://www.fda.gov/bbs/topics/NEWS/NEW00434.html (last visited Oct. 12, 2005).

[233] U.S. National Library of Medicine and the National Institutes of Health, Medline Plus: Tacrine, *available at* http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202722.html (last visited Oct. 12, 2005).

[234] Alzheimer's Disease Education & Referral Center, Alzheimer's Disease Medications Fact Sheet, *available at* http://www.alzheimers.org/pubs/medications.htm (last visited Oct. 12, 2005).

[235] *Id.*

[236] *See* Hilts, Protecting America's Health, *supra* note 34 at 321-22.

[237] Ralph A. Epstein *et al.*, *Advancing Medical Innovation: Health, Safety and the Role of Government in the 21st Century*, The Progress & Freedom Foundation (1996) (available on line at http://www.pff.org/issues-pubs/books/960201advancingmedical.pdf (last visited Sept. 7, 2005)).

[238] *Id.* at 1.

[239] *Id.* at 9-10.

[240] 21 U.S.C. § 379(g)(2)(B) (1998) (stipulating that fees "shall only be collected and available . . . for the process for the review of human drug applications . . . .").

[241] 21 U.S.C. § 379h(f)(1) (1998).

[242] Margaret Gilhooley, *The Administrative Conference and the Progress of Food and Drug Reform*, 30 Ariz. St. L.J. 129, 141, n.60 (1998) [hereinafter, Gilhooley, *Progress of Food and Drug Reform*] (citing *FDA Reform/PDUFA Legislative Package to be Ready by May*, F-D-C Rep. (The Gray Sheet) (Mar. 24, 1997) (quoting Sen. Jeffords, Chair of the Senate Labor and Human Resources Committee, stating that linking user fees to an FDA reform bill "is probably the biggest incentive that I have to get [the FDA] to be very enthusiastic about helping us to get the rest of the package done.")).

[243] In the case of low- to moderate-risk medical devices, the FDAMA permitted companies to select a third party review organization that meets FDA criteria. *See id.* at 134; 21 U.S.C. § 360m (1998). The agency would then

contract with the selected private review organization to undertake the review work that FDA staff would otherwise have performed. *Id.* FDA retained the authority to make changes from the classifications made by reviewers provided it issue a statement explaining the reasons for the change. *Id.*

[244] 21 U.S.C. § 356; Salbu, *supra* note 173 at 121; Deborah G. Parver, Note, *Expediting the Drug Approval Process: An Analysis of the FDA Modernization Act of 1997*, 52 Admin. L. Rev. 1249, 1261 (1999).

[245] FDA Modernization Act, Pub. L. No. 105-115, § 119, 111 Stat. 2317, *codified at* 21 U.S.C. § 355(b)(5)(B).

[246] Salbu, *supra* note 173.

[247] U.S. Food and Drug Administration, News Release, FDA Announces Withdrawal of Fenfluramine and Dexfenfluramine (Fen-Phen) (Sept. 15, 1997) (available online at: http://www.fda.gov/cder/news/phen/fenphenpr81597.htm (last visited Sept. 8, 2005)) [hereinafter FDA News Release: Fen-Phen Withdrawal].

[248] *See* U.S. Food and Drug Administration, Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux) (Sept. 18, 1997), ¶1, *available at* www.fda.gov/cder/news/phen/fenphenqa2.htm (last visited Sept. 8, 2005)) [hereinafter FDA: Pondimin & Redux Q&A].

[249] *See* Alicia Mundy, Dispensing with the Truth: the Victims, the Drug Companies, and the Dramatic Story Behind the Battle over Fen-Phen (St. Martin's Press, New York 2001), 37, 39.

[250] *See* FDA: Pondimin & Redux Q&A, *supra* note 248 at ¶1.

[251] *See* Mundy, *supra* note 249 at 37.

[252] *See* FDA: Pondimin & Redux Q&A, *supra* note 248 at ¶1.

[253] FDA News Release: Fen-Phen Withdrawal, *supra* note 247.

[254] Feder, *supra* note 42.

[255] David Willman, *How a New Policy Led to Seven Deadly Drugs*, L.A. Times, Dec. 20, 2002, § A.

[256] U.S. Food and Drug Administration, *Safety-Based Drug Withdrawals (1997-2001)*, FDA Consumer Magazine (Jan. – Feb. 2002), *available at* http://www.fda.gov/fdac/features/2002/chrtWithdrawals.html (last visited Sept. 8, 2005) [hereinafter FDA, Drug Withdrawal Chart]; *See also* Mary K. Olson, *Pharmaceutical Policy Change and the Safety of New Drugs*, 45 J.L. & Econ. 615, 616 (2002).

[257] Willman, *supra* note 255.

[258] *Id.*

[259] *Id.*

[260] *Id.*

[261] *Id.*

[262] *Id.*

[263] U.S. Food and Drug Administration, Talk Paper T98-36, Wyeth-Ayerst Laboratories Announces Withdrawal of Duract from the Market, Jun. 22, 1998, *available at*: http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html (last visited Oct. 12, 2005).

[264] Willman, *supra* note 255.

[265] FDA, Drug Withdrawal Chart, *supra* note 256; *See also* Willman, *supra* note 255.

[266] Willman, *supra* note 255.

[267] *Id.*

[268] *Id.*

[269] *Id.* (quoting Dr. Robert Califf, Professor of Medicine, Duke University).

[270] *Id.*

[271] *Id.*

[272] *Id.*

[273] FDA, Drug Withdrawal Chart, *supra* note 256; Willman, *supra* note 255.

[274] Willman, *supra* note 255.

[275] *Id.*

[276] *Id.*

[277] *Id.*

[278] *Id.* (quoting Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration).

[279] *Id.*

[280] U.S. Food and Drug Administration, Talk Paper, T00-14, Janssen Pharmaceutica Stops Marketing Cisapride in the US (Mar. 23, 2000), *available at*: http://www.fda.gov/bbs/topics/ANSWERS/ANS01007.html (last visited Oct. 13, 2005); *See also* FDA, Drug Withdrawal Chart, *supra* note 256.

[281] Gina Kolata & Edmund L. Andrews, *Anticholesterol Drug Pulled After Link with 31 Deaths*, N.Y. Times, Aug. 9, 2001, § A.

[282] Philip J. Hilts, *Drug's Problems Raise Questions on Warnings*, N.Y. Times, Aug. 21, 2001, § F [hereinafter, Hilts, *Drug's Problems Raise Questions on Warnings*].

[283] Kolata & Andrews, *supra* note 281.

[284] Hilts, *Drug's Problems Raise Questions on Warnings*, *supra* note 282.

[285] *Id.*

[286] *Id.*; Kolata & Andrews, *supra* note 281.

[287] Hilts, *Drug's Problems Raise Questions on Warnings*, *supra* note 282.

[288] *Id.*; *See also* U.S. Food and Drug Administration, Baycol Information, *available at* http://www.fda.gov/cder/drug/infopage/baycol/default.htm (last visited Oct. 13, 2005).

[289] FDA, Drug Withdrawal Chart, *supra* note 256; *See also* Hilts, *Drug's Problems Raise Questions on Warnings*, *supra* note 282.

[290] FDA, Drug Withdrawal Chart, *supra* note 256.

[291] Olson, *supra* note 256 at 616-17 (2002) (citing O.M. Bakke, *et al.*, *Drug Safety Discontinuations in the United Kingdom, the United State, and Spain from 1974 through 1993: A Regulatory Perspective*, 58 Clinical Pharmacology & Therapeutics 108 (1995)).

[292] *Id.* at 615.

[293] *Id.*

[294] *Id.* at 621.

[295] *Id.*

[296] *Id.*

[297] U.S. General Accounting Office, GAO-02-958, Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals and Other Agency Activities, 26 (2002) [hereinafter, GAO: PDUFA User Fees].

[298] Noah, *supra* note 164 at 465.

[299] *Id.*

[300] 21 C.F.R. § 314.50(d)(5)(iv) (requiring drug sponsors to submit a description and analysis of "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from . . . commercial marketing experience . . . .).

[301] Noah, *supra* note 164 at 465.

[302] The National Academies Institute of Medicine, Committee on the Assessment of the U.S. Drug Safety System, Meeting One, 65-66 (Jun. 8, 2005) (transcript available at http://www.iom.edu/event.asp?id=26964 (last visited Oct. 5, 2005)) [hereinafter, IOM Drug Safety Meeting One] (statement of Alan Goldhammer, Associate Vice President for Regulatory Affairs, PhRMA).

[303] *See FDA, Merck and Vioxx Hearings* (Dr. Bruce Psaty), *supra* note 12 at 2 (discussing Merck's conflict of interest with respect to evaluating whether and when to withdraw Vioxx).

[304] Noah, *supra* note 164 at 475 (citing Michael D. Green, Bendectin and Birth Defects: The Challenges of Mass Toxic Substances Litigation 54-56 (1996)). *See also* Frontline Interview, Dr. Raymond Woosley, *supra* note 172 (stating that, "[t]here's no incentive for a pharmaceutical company to study the serious side effects of medications. They won't do comparative studies when they're going to lose.")

[305] *See supra* note 40 and accompanying text.

[306] *See* Curran, *supra* note 36 (reporting that plaintiff Frederick "Mike" Humeston suffered a heart attack, while taking Vioxx, during the label change negotiations between Merck and FDA).

[307] IOM Drug Safety Meeting One at 77 (statement of Alan Goldhammer, PhRMA).

[308] *See Vioxx Timeline*, *supra* note 35.

[309] *See* Jon Hurdle, *Plaintiff Takes Stand in Vioxx Trial*, Reuters, Sept. 28, 2005.

[310] *See*, *e.g.*, *id.*

[311] Alex Berenson, *A Lawyer's Stock Rises with Victory over Merck*, N.Y. Times, Aug. 22, 2005, C-1.

[312] Help Efficient, Accessible, Low-cost, Timely Healthcare (HEALTH) Act of 2005, H.R. 534, 109th Cong. § 7(c).

[313] *Id.*, §§ 7(c)(1)(A)(i)(I),(II).

[314] *See* text accompanying notes 166-172.

[315] Robert Pear, *Drug Companies Increase Spending on Efforts to Lobby Congress and Governments*, N.Y. Times, Jun. 1, 2003.

[316] IOM Drug Safety Meeting One at 77 (statement of Alan Goldhammer, PhRMA).

[317] FDA's former Chief Counsel Dan Troy sought to accomplish a similar objective through the courts, by seeking to preempt tort suits against drug manufacturers. Before being appointed to the Chief Counsel position by President George W. Bush, Troy had sued FDA on behalf of the Washington Legal Foundation, the group that proclaimed, during the Gingrich-era attacks on the agency: "If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious." *See* text accompanying note 216. For a discussion of the Troy-era assertions by FDA of the preemption defense on behalf of drug manufacturers, *see* Margaret H. Clune, *Stealth Tort Reform: How the Bush Administration's Aggressive Use of the Preemption Doctrine Hurts Consumers*, Center for Progressive Reform White Paper No. 403, *available at* http://www.progressiveregulation.org/articles/preemption.pdf (last visited Oct. 5, 2005).

[318] Shuren, *supra* note 146 at 308-09 (detailing FDA's 1973 conditioning approval of Levodopa on Phase IV testing).

[319] *Id.* at 314.

[320] *Id.* at 315 (citing 21 U.S.C. § 356(b)).

[321] *Drug Safety on Trial*, *supra* note 34; *see* U.S. Food and Drug Administration, *Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies; Availability*, Table 1: Summary of Postmarketing Study Commitments (Numbers as of September 30, 2004), 70 Fed. Reg. 8379, 8380 (February 18, 2005).

[322] Letter from Larry Sasich, *et al.*, Public Citizen Health Research Group, to Jane Henney, Commissioner, FDA (April 13, 2000) (available online at http://www.citizen.org/publications/print_release.cfm?ID=6721).

[323] *Drug Safety on Trial*, *supra* note 34.

[324] 21 U.S.C. § 356b(d).

[325] 21 U.S.C. § 356b(e). As argued by the Public Citizen Health Research Group, a more effective means of ensuring that drug sponsors honor Phase IV commitments would be to authorize FDA to levy substantial civil monetary penalties against delinquent companies. Letter from Larry Sasich, *et al.* to Jane Henney, *supra* note 322.

[326] U.S. Food and Drug Administration, MedWatch: What is a Serious Adverse Event?, *available at* http://www.fda.gov/medwatch/report/DESK/advevnt.htm (last visited Oct. 18, 2005).

[327] *Id.*

[328] Noah, *supra* note 164 at 466.

[329] *Id.* at 469 (citing 21 C.F.R § 314.80 (1999)).

[330] *Id.* at 470; *See* 21 C.F.R. § 314.80(c)(1)(i). "Serious" adverse drug experiences include: "death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, [or] a persistent or significant disability/incapacity." 21 C.F.R. § 314.80(a). An "unexpected" event is "[a]ny adverse drug experience that is not listed in the current labeling for the drug product." *Id.*

[331] Noah, *supra* note 164 at 469.

[332] U.S. Food and Drug Administration, What is MedWatch?, *available at* http://www.fda.gov/medwatch/What.htm (last visited Oct. 18, 2005).

[333] *Id.*

[334] Noah, *supra* note 164 at 469.

[335] *Drug Safety on Trial*, *supra* note 34.

[336] Kessler, *Introducing MedWatch*, *supra* note 168 (citing H. D. Scott, *et al.*, *Rhode Island Physicians' Recognition and Reporting of Adverse Drug Reactions*, 70 R.I. Med. J. 311, 311-16 (1987)).

[337] *Id.* The disinclination to associate an adverse event with a drug may be due to the limited training that medical students receive in pharmacology and therapeutics. *Id.* A 1985 survey of U.S. medical schools found that only 14% had required courses in core skills and principles of therapeutic decision-making and clinical pharmacology. *Id.* (citing D.W. Nierenbert, *Clinical Pharmacology Instruction for All Medical Students*, 40 Clinical Pharmacology & Therapeutics 483, 483-87 (1986)). Of the remaining schools, 87% taught only a few hours of clinical pharmacology, usually in the early years of medical training. *Id.*

[338] Meredith Wadman, *The Safety Catch*, 434 Nature 554, 556 (2005); *see also* Kessler, *Introducing MedWatch, supra* note 168 at 2768; Moore, *et al.*, *supra* note 171 at 1572 (explaining that the spontaneous reporting system fails when a drug causes an event that might be expected as part of the natural history of the disease being treated).

[339] Moore, *et al.*, *supra* note 171 at 1572.

[340] *Id.* at 1571.

[341] Institute of Medicine of the National Academies, Assessment of the U.S. Drug Safety System, *available at* http://www.iom.edu/project.asp?id=26341 (last visited Oct. 4, 2005); See also *FDA, Merck and Vioxx Hearings* (Dr. Sandra Kweder) *supra* note 24 at 5.

[342] Frontline Interview, Dr. Raymond Woosley, *supra* note 172 (stating that "the number of people hired at the agency to protect, to analyze data and drug safety is criminal . . . . [t]he teams that are needed to do drug safety are infinitely more than what they've got right now" and that "[t]he system works, it's just too slow . . . . [w]e have to do too much else to verify that a signal is real, because we don't have the other tools.") .

[343] Interview by Frontline with Paul Seligman, M.D., M.P.H., Director, FDA Office of Pharmacoepidemiology and Statistical Sciences and Director, FDA Office of Drug Safety (Nov. 4, 2002), transcript available at: http://www.pbs.org/wgbh/pages/frontline/shows/prescription/interviews/seligman.html (last visited Aug. 18, 2005).

[344] Noah, *supra* note 164 at 473.

[345] 21 U.S.C. § 379h(g)(1) (1998) (stipulating that fees "shall be available solely for the process for the review of human drug applications . . . ."); 21 U.S.C. § 379h(g)(2)(B) (1998) (stating that fees " shall only be collected and available to defray increases in the costs of resources allocated for the process for the review of human drug applications . . . over such costs, excluding costs paid from fees collected under this section, for fiscal year 1997 multiplied by the adjustment factor).

[346] Harris, *Regulation Redefined*, *supra* note 50.

[347] GAO: PDUFA User Fees, *supra* note 297 at 17.

[348] *Id.*

[349] *Id.* Although FDA received a number of funding increases since enactment of PDUFA, "almost all funding increases received since 1992 were earmarked for designated programs." *Id.* at 18.

[350] Harris, *Regulation Redefined*, *supra* note 50.

[351] CDER's costs for the review of human drug applications in FY2002 were $209,823,215. U.S. Food and Drug Administration, FY2002 PDUFA Financial Report, 9 (2003), *available at* http://www.fda.gov/cder/pdufa, FDA PDUFA Page, Annual Reports and Plans: Financial (last visited Oct. 18, 2005). CDER's program level funding, including appropriated funds and user fees, was $282,000,000. *Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations for 2006: Hearing Before a Subcommittee of the House Comm. on Appropriations.,* 109th Cong. 807 (2005) (statement of Lester M. Crawford, Acting Commissioner of the Food and Drug Administration) [hereinafter, CDER Funding Table, FY'96-FY'06].

[352] CDER Funding Table, FY'96-FY'06, *supra* note 350.

[353] *Drug Safety on Trial*, *supra* note 34; Harris, *Regulation Redefined*, *supra* note 50.

[354] Harris, *Regulation Redefined*, *supra* note 50 (quoting Dr. Lou Cantilena, head of the division of clinical pharmacology and medical toxicology at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, which helped the agency study drug safety issues and trained its staff prior to the late 1990s).

[355] *See* GAO: PDUFA User Fees, *supra* note 297 at 28 (stating that "[h]istorically, the vast majority of adverse effects have been identified in the first 2 to 3 years after a new drug is marketed); *See also* text accompanying notes 166-172.

[356] Noah, *supra* note 164 at 451 (citing, *inter alia*, Charles Marwick, *Drug Safety Takes Cooperation*, 282 JAMA 315, 316 (1999)).

[357] Stuart Elliott, *Advertising: With or Without Vioxx, Drug Ads Proliferate*, N.Y. Times, Dec. 6, 2004, § C.; *The Experts' Verdict on Painkillers*, *supra* note 43.

[358] Elliott, *supra* note 356.

[359] Julie Schmit, *A Winded FDA Races to Keep Up with Drug Ads That Go Too Far*, USA Today, May 31, 2005.

[360] CDER Funding Table, FY'96-FY'06, *supra* note 351.

[361] GAO: PDUFA User Fees, *supra* note 297 at 18.

[362] Merrill, *supra* note 186 at 1795-96, n. 131; *See also* Pub. L. 107-188 §502(4), 116 Stat. 688 (stating that fees "will be dedicated towards expediting the drug development process and the process for the review of human drug applications as set forth in the goals" identified in a letter to the Congress from the Secretary of the Department of Health and Human Services) .

[363] FDA Modernization Act, Pub. L. No. 105-115, § 119, 111 Stat. 2317, *codified at* 21 U.S.C. § 355(b)(5)(B). For specific performance goals under PDUFA II, and how, in the case of those related to the review of drug applications, they compare to those established in conjunction with the initial user fee act, *see* GAO: PDUFA User Fees, *supra* note 297 at 19.

[364] *Id.*

[365] *Id.*

[366] *Id.* at 19-20. Six disciplines are typically involved in reviewing NDAs, and are represented by medical officers, chemists, microbiologists, statisticians and pharmacologists/toxicologists. *Id.*

[367] *Id.* at 21.

[368] *Id.*

[369] *Id.* at 23.

[370] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, Title V, 116 Stat. 687-97.

[371] *Id.*, 116 Stat. 688 (adding "strengthening and improving the review and monitoring of drug safety" to section stating that PDUFA should be reauthorized and carried out by FDA "with new commitments to implement more ambitious and comprehensive improvements in regulatory processes"). *Cf.* FDA Modernization Act, Pub. L. No. 105-115, Title I, § 101(3)(B), 111 Stat. 2298 (containing identical language regarding improvements in regulatory processes, but lacking examples).

[372] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, Title V, §§ 504(f)(1),(2), 116 Stat. 691, 21 U.S.C. §§ .379h(g)(1), (2)(A)(ii).

[373] *Id.*, 116 Stat. 688; 21 U.S.C.A. § 379g(6)(F).

[374] GAO: PDUFA User Fees, *supra* note 297 at 27-28.

[375] *Id.* at 28.

[376] *Id.*

[377] U.S. Food and Drug Administration, PDUFA III Five-Year Plan, 16 (*CDER Plan Summary Tables – PDUFA III Plan for Funds from PDUFA Fee Revenues*) (July 2003), *available at* http://www.fda.gov/oc/pdufa3/2003plan/default.htm (last visited Oct. 9, 2005) (estimating five-year expenditures of $56,137,000 for risk management, out of five-year total expenditures of $732,113,000).

[378] *President's Fiscal Year 2006 Budget for the U.S. Department of Health and Human Services: Hearing Before the House Comm. on Ways and Means*, 109th Cong. (statement of the Hon. Michael O. Leavitt, Secretary, U.S. Department of Health and Human Services); *See also* CDER Funding Table, FY'96-FY'06, *supra* note 351.

[379] CDER Funding Table, FY'96-FY'06, *supra* note 351.

[380] Compare U.S. Food and Drug Administration, PDUFA Reauthorization Performance Goals and Procedures, *available at* http://www.fda.gov/cder/pdufa/default.htm (last visited Oct. 9, 2005) *with* GAO: PDUFA User Fees, *supra* note 297 at 19 (summarizing major performance goals under PDUFA II).

[381] Wadman, *supra* note 337 at 556 (quoting former FDA Commissioner David A. Kessler). Former Commissioner Kessler also remarked that post-market safety monitoring "absolutely needs more resources. You just can't have resources go into new drug review." *Id.*

[382] Rep. Maurice Hinchey's proposed FDA Improvement Act proposes to eliminate the current user fee program, requiring instead that all industry fees be deposited in the general fund of the Treasury. Food and Drug Administration Improvement Act of 2005, H.R. 2090, 109th Cong. § 740(a) [hereinafter, FDAIA].

[383] *See, e.g.*, *id.* at § 740B(a)(1)(A) (terminating FDA's authority to enter into agreements, including performance goals, with persons from whom fees are collected).

[384] Letter from Larry Sasich, *et al.*, to Jane Henney, *supra* note 322.

[385] *See*, *e.g.*, *Drug Safety on Trial*, *supra* note 34; *see also* FDAIA, *supra* note 381 at § 4 (proposing to amend the Federal Food, Drug and Cosmetic Act by deeming "misbranded" drugs whose labels fail to include specific wording required by FDA in order to ensure their safe and effective use).

[386] *See, e.g.*, Moore, *et al.*, *supra* note 171 at 1572.

[387] Phenylpropanolamine (PPA) was in use prior to 1962, when the Kefauver-Harris amendments required a review of the effectiveness of this and other drugs while they remained on the market. U.S. Food and Drug Administration, FDA Consumer Magazine (Jan.-Feb. 2002). In November 2000, due to a demonstrated association between PPA and hemmorhagic stroke, FDA requested that companies discontinue marketing products containing the drug. U.S. Food and Drug Administration, Talk Paper, T00-58, FDA Issues Public Health Warning on Phenylpropanolamine (Nov. 6, 2000), available at http://www.fda.gov/bbs/topics/ANSWERS/ANS01051.html (last visited Oct. 20, 2005).

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*Inside:*

*A Center for Progressive Reform White Paper*

# *The Hidden Lesson of the Vioxx Fiasco: Reviving a Hollow FDA*

*by Rena Steinzor and Margaret Clune*

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