Pharmaceutical Regulation in the United States: A Confluence of Influences[1]

By Reuben A. Guttman[2]

Background

Pharmaceuticals, like other consumer products distributed in the United States, are subject to regulation and scrutiny from multiple sources. Legislative oversight and statutory pronouncement, regulatory mandate and oversight, judicial review, and non-governmental organization (NGO) and media oversight directly and/or indirectly impact the conduct of pharmaceutical manufacturers. In addition, stakeholders including pharmaceutical company shareholders, employees of pharmaceutical companies, and those entities that ultimately bear the costs of paying for drugs – known as third-party payors –also influence the conduct of drug manufacturers.

For example, the securities markets that price stock rely, in part, on representations that drug companies make about the integrity of their products. Public misrepresentations to regulatory bodies and/or consumers also play out indirectly as misrepresentations to shareholders resulting in additional liability for companies and those individuals who run them. Accordingly, shareholders – the owners of the pharmaceutical companies – have an interest in ensuring not only the integrity of products sold to consumers, but the integrity of public statements about their products.[3]

Through their retirement plans, pharmaceutical company employees invest in their employer and, to some degree, stand in the same shoes as shareholders except that they have rights of redress under United States Pension laws.[4] Product recalls result in diminished stock value and lost savings for employees who invest in their companies.

Third-party payors, including labor union health and welfare funds, State Medicaid and employee health and welfare funds, and the federal Medicare system, have also had an immense impact with regard to the conduct of the pharmaceutical industry.

To say that any one of these influences is the real source of regulation would paint an incomplete picture. It is the totality of these influences, and their interplay with each other, that either impact or have the potential to impact manufacturer conduct.

Legislation, Regulation, and Oversight

The Food, Drug and Cosmetics Act and the regulations

In the United States, legislative intervention in the sales of drugs dates back to 1938 with the initial passage of the Food, Drug & Cosmetics Act (FDCA).[5] Like many laws promulgated by the Congress of the United States, the FDCA created an "expert" agency known as the Food and Drug Administration (FDA) which is empowered to create specific, and somewhat technical regulations, governing the sales of food and drugs. Expert agencies, such as the FDA, are established by Congress because of the legislature's inability to practically micromanage thousands of products. Aside from its regulation of food and medical devices, the FDA regulates more than 11,000 drugs.[6]

The FDA is both a regulatory and an adjudicatory agency. It makes regulations that further the mission of the FDCA and it makes decisions, i.e., adjudications, about the specific application of its regulations.[7]

A manufacturer seeking to market a drug must apply for an "indication," which is a term used to define the parameters for which the drug is approved for use. Before marketing and selling a prescription drug, a manufacturer must demonstrate to the FDA that the product is safe and effective for its intended use.[8] The FDA does not give blanket approvals for the use of a drug. Rather, the agency approves a drug for specific uses which may mean the treatment of a disease or just symptoms attributable to the disease. The indication may be limited in that the drug may only be used in combination with other specifically identified drugs or at a specific stage of the disease. The indication may also be limited as to dose or how the dose may be administered. [9]

Once the FDA approves an indication, the manufacturer provides the FDA

with a package insert for approval. The package insert will set forth the indication and will also list side effects, warnings, and dosing information. In theory, the package insert is a dynamic document, meaning that it subject to change based on experiences from the actual use of the drug. Manufacturers are required to report "adverse" events to the FDA and based – in part – on adverse events, the package insert is updated with additional warnings. The most serious warning mandated by the FDA is the "Black Box" warning which is a warning enclosed by a black box. A Black Box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening effects.

The FDA regulates both prescription and over the counter drugs. Prescription drugs can only be acquired from a pharmacy after the pharmacy is handed a prescription written by a doctor. In the United States, doctors must be licensed to write a prescription and each prescription must cite the doctor's license number. Significantly, the FDA regulates the conduct of manufacturers; it does not regulate doctors. While doctors are made aware of a drug's indication, they are not required to write prescriptions for purposes and uses within the boundaries of the indication. The use of a drug for purposes that fall outside the indication is known as an "off-label use." Doctors are free to write prescriptions for off-label uses. In contrast, with the exception of purely scientific, medical information provided by qualified medical professionals, sales and marketing presentations, promotions, or marketing by drug companies to physicians for uses other than that approved by the FDA is considered off-label marketing and is proscribed by law.[10]

When marketing a drug, the FDCA also requires that the manufacturer be truthful about its product. Pharmaceutical promotion and marketing materials and presentations lacking in fair balance or that are otherwise false and misleading violate the FDCA[11] and regulations promulgated by the FDA pursuant to the statute. Such violations exist where promotional and marketing materials and presentations for the FDA approved drug:

- Minimize, understate, or misrepresent the risks, contra-indications, and complications associated with that drug;

- Overstate or misrepresent the risks, contra-indications, and complications associated with any competing drugs;

- Reference "off-label" uses of the drug - i.e., those uses which are not indicated by the FDA - or expressly or implicitly promote unapproved uses and dosing regimens for which the drug is not indicated;

- Make comparative claims about the drug which have not been demonstrated by substantial evidence, such as comparisons with competing drugs and/or drug indications of patient usage, warnings and safety claims including side effects, physician preference, or

- Are otherwise false, misleading or lacking in fair balance in the presentation of information about the drug being marketed or any competing drug.

Congressional Oversight

The American system is replete with checks and balances. While the United States Congress promulgated the FDCA, which in turn established the FDA, Congress continues to engage in oversight of the agency and situations that might call for a change in the law or merely the exposure of a problem.

Oversight can take the form of formal hearings that are open to the public or less formal inquiries made by members of Congress to government agencies or private sector entities. In October 2008, for example, Charles Grassley, a United States Senator from the State of Iowa, initiated an investigation over conflicts of interest involving studies conducted by Charles Nemeroff, a Professor of Medicine at Emory University in Atlanta who allegedly earned more than $2.5 million dollars in side payments from the pharmaceutical industry while he was studying the safety and efficacy of certain drugs.

Senator Grassley's investigation lead to Professor Nemeroff's suspension from a portion of his tasks by Emory University and generated a wave of media inquiry and oversight, placing additional focus on whether studies conducted under the auspices of universities are tainted by conflicts of interests resulting from payments to university professors by the pharmaceutical industry.[12]

Senator Grassley's intervention with regard to Nemeroff and Emory publicly began with a September 16, 2008 letter to Emory University President James Wagner. The letter is instructive in that it outlines the Senate oversight process as it applied to Nemeroff and Emory's conduct.

> Dear Dr. Wagner:
>
> The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage under these programs. As Ranking Member of the Committee, I have a duty to protect the health of Medicare and Medicaid beneficiaries and safeguard taxpayer dollars

appropriated for these programs. The actions taken by key experts often have profound impact upon the decisions made by taxpayer funded programs like Medicare and Medicaid and the way that patients are treated and funds expended.

Moreover, and as has been detailed in several studies and news reports, funding by pharmaceutical companies may influence scientific studies, continuing medical education, and the prescribing patterns of doctors. Because I am concerned that there has been little transparency on this matter, I have sent letters to almost two dozen research universities across the United States. In these letters, I asked questions about the conflict of interest disclosure forms signed by some of their faculty. Universities typically require doctors to report their related outside income, but I am concerned that these requirements are disregarded sometimes.

I have also been taking a keen interest in the almost $24 billion annually appropriated to the National Institutes of Health (NIH) to fund grants at various institutions such as yours. As you know, institutions are required to manage a grantee's conflicts of interest.1 But I am learning that this task is made difficult because physicians do not consistently report all the payments received from drug companies.

To bring some greater transparency to this issue, Senator Kohl and I introduced the Physician Payments Sunshine Act (Act). This Act will require pharmaceutical companies to report publicly any payments that they make to doctors, within certain parameters.

The purpose of this letter is to assess the implementation of financial disclosure policies at Emory University (Emory/ the University). In response to my letter of October 25, 2007, Emory provided me with the financial disclosure reports that Dr. Charles Nemeroff filed with Emory during the period of January 2000 through June 2007. Dr. Nemeroff is the Reunette W. Harris Professor and Chairman of the Department of Psychiatry and Behavioral Sciences at Emory and is one of the most widely published experts in the field of psychiatry.

My staff investigators carefully reviewed each of Dr. Nemeroff's disclosure forms and detailed the payments disclosed. I then asked that Emory confirm the accuracy of the information my staff compiled. In March 2008, Emory clarified previous statements and provided a chart of Dr. Nemeroff's outside income. This chart contained several reports of, among other things, Dr. Nemeroff's outside consulting that my staff did not find in his disclosure forms filed with Emory.

In addition, I contacted executives at several major pharmaceutical and device companies (the Companies) and asked them to list the payments that they made to Dr. Nemeroff during the years 2000 through 2007. These companies voluntarily and cooperatively reported additional payments that Dr. Nemeroff does not appear to have disclosed to Emory. For example, Dr. Nemeroff disclosed receiving $7,500 in 2005 from Pfizer. But Pfizer reported to me that it paid Dr. Nemeroff $138,000 in speaker honoraria (at least 40 speaking engagements) and consulting fees that same year. Based upon the information provided to me from both Emory and the Companies, it also appears that Dr. Nemeroff failed to disclose the vast majority of the over $900,000 that he received in speaking fees and expenses related to talks he has given on behalf of GlaxoSmithKline (GSK).

Because Dr. Nemeroff's disclosures to Emory differ dramatically from those that I received from the Companies, I am attaching a chart that best represents a few of the disclosures made to me by the Companies. Specifically, the attached chart contains columns showing some of the payments disclosed by Dr. Nemeroff in March 2008 contrasted with the amounts reported to me by the Companies. However, I understand that some discrepancies may exist because Emory is uncertain if the disclosures were made during a calendar year or academic year.[13]

On October 2, 2008, Senator Grassley wrote a second letter to Emory President Wagner providing supplemental information related to his committee's investigation and informing President Wagner that while conducting research on the safety and efficacy of various drugs pursuant to a government grant that Emory had received, it was clear Dr. Nemeroff was separately receiving money from the pharmaceutical industry. A third letter written by Senator Grassley to the Inspector General of the U.S. Department of Health & Human Services, dated February 24, 2009, brought this matter to that agency's

attention, for the purposes of prompting an investigation by the Inspector General's office.

The Grassley inquiries with regard to Nemeroff were significant because the legitimacy of trials or studies conducted by universities – with government grants – is of critical importance to the integrity of the FDA's regulatory system, as these works are often the basis of decision making by the FDA in regulating prescription drugs. These studies and/or trials are used by the pharmaceutical industry when applying to the FDA for a new drug indication or an expanded indication.

The Grassley letters are not unique. The United States Congress, through its oversight committees, continuously monitors the conduct of the FDA and the pharmaceutical industry. Oversight is not always done for purely public interest reasons. For example, oversight of the FDA may be inspired by a party that is out of power in the Executive Branch, of which the FDA is a part. Or, oversight may be conducted at the behest of one pharmaceutical company which has secured the aid of a member of Congress to question the conduct of a competitor or the FDA's treatment of a competitor or, for that matter, its own product. Still, there are members of Congress who secure a lot of media attention for their efforts to expose wrongdoing in the pharmaceutical industry and this media attention can help maintain a member's popularity for the purposes of re-election. As to which members of Congress tend to get involved in oversight, one reasonable observation is that members tend not to favor investigating companies that provide jobs to citizens in their district.

The Tort System

Notwithstanding that the FDA is supposed to be an expert agency, the task of regulating 11,000 drugs, thousands of devices, and food, is so vast that some mistakes are inevitable in oversight and compliance enforcement. There are multiple examples of where drugs given an indication by the FDA have later been found to be defective. These drugs have either been voluntarily withdrawal from the market, withdrawn at the behest of the FDA or, in some cases, maintained on the market but with additional warnings including the most serious warning, the FDA mandated "Black Box Warning."

For example, after multiple adverse events involving the drug, Trasylol, which was used in coronary bypass surgery, the drug was withdrawn from the market by its manufacturer, Bayer AG, in 2007.[14] Similarly, the drug Bextra was approved by the FDA in 2001 for several uses including those related to the treatment of rheumatoid arthritis. Bextra was withdrawn from the market in 2005. Though not implicating a withdrawal from the market, possible evidence of diabetes related to the use of the drugs Zyprexia, Risperdal, and Seroquel – all atypical antipsychotics – lead to Black Box warnings being imposed by the FDA on each of those drugs.

In each of the above cases, Trasylol, Bextra, Zyprexia, Risperdal, and Seroquel, the manufactures have been faced with common law "tort" actions brought by individuals who allegedly have been harmed by the drugs. These common law actions have been able to proceed because in promulgating the FDCA, a federal law, the United States Congress did not pre-empt the right of private citizens to bring these types of actions under state law. The question of whether the FDCA preempts these types of actions was addressed by the United States Supreme Court in *Wyeth v. Levine*.[15]

Wyeth is a large pharmaceutical company[16] that manufactures the anti-nausea drug, Phenergan. The cause of action arose after a patient, Diana Levine, was administered the drug intravenously though the "IV Push" method – one method of administration[17] – which risks that the Phenergan may enter an artery, causing gangrene and the loss of a limb. The drug is highly corrosive and causes irreversible gangrene if it enters a patient's artery.

Diana Levine had a career as a guitar player until the administration of Phenergan through the IV Push method lead to the drug entering her artery causing Gangrene and the loss of her arm. Levine filed a lawsuit in a Vermont State Court against Wyeth asserting common law negligence and strict liability theories. As explained by the Court: "Although Phenergan's labeling warned of the danger of Gangrene and amputation following inadvertent intra-arterial injection, Levine alleged that the labeling was defective because it failed to instruct clinicians to use the IV-drip method of intravenous administration instead of the higher risk IV-push method."[18] Levine framed her legal claims in accustomed tort law terms, as follows: "More broadly, she alleged that Phenergan is not reasonably safe for intravenous administration because of the foreseeable risks of gangrene and loss of limb are great in relation to the drug's therapeutic benefits."[19] At trial, Wyeth argued, among other things, that it had submitted its label to the FDA for approval, the agency approved the label and, hence, Wyeth could not be held liable. A jury returned a verdict of $7.4 million, which the trial judge partially reduced to account for Levine's earlier out of court settlements with a health care center and a clinician.

After the jury returned its verdict, Wyeth petitioned the trial judge to reject the verdict because Levine's cause of action was "pre-empted" by FDA regulation of pharmaceuticals. Wyeth claimed that the FDA, a federal agency implementing a federal law, was solely

responsible for regulating Wyeth's labeling and thus any intervention by the courts of the State of Vermont would interfere with that authority.[20] Finding no conflict between FDA regulation and Levine's common law claims, the trial court let the verdict stand.

In an appeal to the Vermont Supreme Court, that Court affirmed the trial court judgment opining that the jury verdict "did not conflict with FDA labeling requirements for Phenergan because [Wyeth] could have warned against the IV-push administration without prior FDA approval, and because federal labeling requirements create a floor, not a ceiling, for state regulation."[21] The importance of the pre-emption issue coupled with the FDA's position that its regulation pre-empted Levine cause(s) of action resulted in the United States Supreme Court agreeing to hear the case.

Finding against Wyeth and the FDA's position,[22] the United States Supreme Court affirmed the decision of the Vermont Supreme Court, which upheld the jury verdict. Of particular interest is a quote from the Court's opinion (Stevens, J.), which explained that the position taken by the agency in the *Levine* case was contrary to the intent of the FDCA and longstanding positions taken by the FDA,[23] as follows:

> In keeping with Congress' decision not to pre-empt common-law tort suits, it appears that the FDA traditionally regarded state law as a complementary form of drug regulation. The FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the post-marketing phase as new risk emerge. State tort suits uncover unknown drug hazard and provide incentives for drug manufacturers to disclose safety risk promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure to warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.[24]

To restate the Court's position in a slightly different way, the significance of common law actions are multi-fold. First, as noted, they bring relief to the victims. Second, to the extent that companies are required to pay out large sums of money to victims, the price of their stock may drop leading to additional pressure in the form of shareholder securities and derivative[25] litigation against the company and members of the company's board of directors. Pfizer and Merck pharmaceuticals which had to pay out large sums of money to victims of their Cox-2 inhibitor drugs, Vioxx and Bextra, were both targeted by shareholder securities lawsuits. In these cases, the shareholders alleged that the companies withheld information from the securities markets and that their billion dollar products caused serious side effects. Had shareholders been made fully aware of the problems with these drugs, they arguably would not have invested in their manufacturers.

Perhaps most important is the role of the tort litigation in providing a transparent record for lawmakers, regulators at the FDA and the medical professional.[26] In American civil procedure, these suits, which begin with a formal complaint outlining the Defendant's wrongdoing and the damage it caused, are met with a written answer by the Defendant. Once the court determines as a legal matter that the facts as alleged state a "cause of action,"[27] the "discovery" process moves forward where the parties exchange documents, and witnesses are called to testify in depositions. In the Spring of 2009, discovery in litigation against the drug manufacturer, Astra Zeneca, involving side effects from its drug, Seroquel, surfaced a document known simply as "Study 15" which exposed questions about the Seroquel's safety and efficacy. Although Astra Zenaca had actually provided this study to the FDA, the agency, failing to act on it or take notice of its significance, was unable to release it to the public because it was a document provided by the company to the FDA in confidence. One of the problems inherent in the FDA process is the agency's inability to properly scrutinize each and every document that is submitted in furtherance of a new drug indication (NDI) or an expanded indication. In protecting the sanctity of these documents as trade secrets, more often than not important documents concerning drugs do not see the light of day and are not subject to public scrutiny.

In the United States, there is no true independent broker for honest information about pharmaceutical products. Billions of dollars are spent on television and print advertising which have two goals: (1) making people aware that they may have an illness, and (2) promoting a product that can address the illness. In many cases, the advertising is targeted to symptoms which are a normal part of the human existence and are not life threatening. Products dealing with urine flow, restless legs, sleep disorders, and depression are marketed directly to consumers with the intent that the consumer will "ask their doctor" to write a prescription.[28] The obvious strategy is to create a ground swell that pressures doctors to write prescriptions. While the advertisements are required

to disclose the side effects of the drugs, the side effects are often recited while the TV picture portrays a happy healthy person playing with his kids, hand in hand with his wife, or in some other happy mode.

Companies also deploy sales representatives who visit doctors and hospitals with pitches explaining why their products – in comparison to competitors' products – are the proper choices. The representatives select doctors to visit based on prescription writing data that their company purchases. Through armies of representatives who give pitches outside the FDA indication, the industry has made a pattern and practice of unlawfully marketing drugs for off-label use.

In addition to information from sales representatives, doctors also can read about the safety and efficacy of drugs in journals, including the *New England Journal of Medicine*, which historically has been one of the most respected publications. Unfortunately, there is now evidence that studies reported in these types of publications have been subject to undue industry influence either because they have been funded by the industry or because doctors conducting the studies have – but did not disclose -- their financial relationship to the industry.

Doctors can also learn about drugs through educational seminars and continuing medical education programs (CME). Here, too, discovery in recent litigation has revealed that the industry has attempted to influence these programs by funding them and selecting doctors who will give a message favorable to their product. When a drug company is sponsoring a CME program, speakers are sometimes chosen -- with input from sales representatives -- based on their ability to influence product sales.

Curiously, perhaps the most honest source of product information comes from companies that – as part of their marketing practices – disclose information about their competitors' products in an effort to undermine their competitor's products' reputation for safety and efficacy. It is, for example, common for pharmaceutical representatives to distribute documents comparing their products to the products of their competitors. These documents highlight safety and efficacy issues with competing drugs. Unfortunately, because these documents are prepared from publically available information, competitors are unable to access information "buried" within the FDA files which actually may shed light on the safety and efficacy of a competitor's product.

The Role of NGOs

Non-governmental organizations (NGOs) have a played a role in exposing flaws in pharmaceutical products and providing expert advice to lawmakers, FDA officials, and healthcare providers. Where warranted, these groups have actually brought litigation against companies and/or the FDA either to seek redress or compel agency action. The United States Supreme Court has long held that public interest groups representing members that might face injury or harm have "standing" to seek redress in court.[29] The ability of these groups to actually file lawsuits against the FDA is yet another check on the system. In the United States, there are multiple NGO's that have had an impact.

The NGO Public Citizen, which was founded by Ralph Nader, for example, constantly reviews information about drugs and publishes a list of what it deems to be the best and worst drugs.[30] Playing off the judicial process, Public Citizen has been instrumental in helping to establish the right of citizens to access non-confidential documents that are produced in the context of "discovery" in court proceedings. In *Public Citizen v. Liggett Group, Inc.*, 858 F.2d 775, 787 (1st Cir 1988), Public Citizen furthered the right of third parties to intervene in litigation to secure non-confidential documents produced in the litigation. Relying on this case, the United States District Court in *U.S. ex rel. Franklin v. Parke Davis*, 210 F.R.D. 257 (D. Mass 2002), allowed the *New York Times* and *Boston Globe* to intervene in the litigation – involving claims about the unlawful marketing of the drug, Neurontin – to secure documents produced in discovery. Quoting the *Liggett* case, the Court in *Franklin* opined that "[p]arties to litigation 'have a general first amendment freedom with regard to information gained through discovery and … absent a valid court order to the contrary, they are entitled to disseminate the information as they see fit."[31]

As a representative of its members, who are consumers, Public Citizen has also played an active role in the FDA process. That role has ranged from filing "petitions" with the FDA seeking the agency's agreement to withdraw a drug from the market to filing lawsuits against the FDA to compel it to do so. For example, in June 2008, Public Citizen sued the FDA in federal court for failing to act on its petition to withdraw the painkillers Darvon, Darvocet and all drugs containing propoxyphene from the market. In doing so, Public Citizen was relying upon a decision made by United Kingdom (U.K.) regulatory authorities in withdrawing these drugs from the market. The U.K. began a phased withdrawal of Darvocet from the British market in 2005, following the recommendation of the U.K. Committee on Safety of Medicines (CSM). In its report, the CSM stated that it could not "identify any patient group in whom the risk-benefit [ratio]

may be positive." The withdrawal was completed at the end of 2007.

Similarly, the Center of Science in the Public Interest (CSPI), another NGO, which has focused on exposing false and misleading advertising, initiated litigation in California Superior (State) Court against Bayer AG for allegedly falsely claiming that the selenium in Men's One A Day multivitamins might reduce the risk of prostate cancer. The suit was filed after CSPI contacted Bayer, asking that the company change its label. In filing its suit, CSPI was relying on state – not federal – law to seek redress.

The Stakeholders

Third-party Payors

The United States does not have a "universal" health care system where every citizen is guaranteed health care. There are a myriad of systems which provide health care coverage but these systems do not come close to providing health care coverage for every citizen.[32] These systems are commonly known in the United States as third-party payors or TPP's. The following are the basic TPP's:

- **The Medicaid system.** Medicaid is administered by states but is funded with state and federal government dollars. It is a program designed to provide health care coverage for those with limited income. Medicaid does not pay money to the individual; rather it pays money to the provider including a doctor, hospital or pharmacy.

- **The Medicare system** was established by the Federal government and is funded with federal dollars. It provides health care coverage to the elderly. It covers only those who paid money into the Medicare system for at least ten years and – absent some disability – is only available when the individual reaches the age of 65. As in the case of Medicaid, Medicare does not pay money to the individual; rather it pays money to provider including a doctor, hospital or pharmacy.

- **Private insurance carriers** which are funded by premiums paid by individuals or their employers also subsidize the cost of health care.

- **Union-Employer health care plans** which are the result of agreements negotiated between labor unions and employers have been established to subsidize the cost of health care. These plans which, at least as to non-governmental employees, are regulated by the Employee Retirement Income Security Act (ERISA),[33] are funded by monetary contributions from the employer and sometimes by partial contributions from employees. The plans either purchase insurance coverage from a private insurance carrier or "self insure" but use an insurance carrier or some other intermediary to disperse payments to health care providers.

- **Government employee health care plans** also exist for state and federal employees. In addition, plans also exist to cover members of the military and their families.

The third-party payors have established systems for the reimbursement or payment of prescription drugs. Insurers, and union-employer plans and employer plans in some cases -working through pharmacy benefit managers (PBMs) – establish formularies which favor(ed) the use of generics or one competitor over another. A favored drug might be reimbursed at a rate of 100% while another competitor – but not favored drug – might be reimbursed at a rate of 50%.

Understanding how the formularies work, the drug companies have strived to make sure that their drugs get favorable formulary treatment. In some cases, the manufacturers have paid kickbacks to the PBM's to ensure that their drugs are included in the formularies. Where the drugs cannot be listed on the formularies, the manufacturers have made coupons available on the internet. These coupons subsidize the cost of the drug that is not borne by the plan. The coupon systems – which are now prevalent in the United States – essentially have been designed by the pharmaceutical industry to undermine the formularies at great cost to third-party payors.

Third-Party Payors Can Take Legal Action

As third-party payors have become more conscious about controlling their costs, the kickbacks schemes have been the subject of litigation. This has particularly manifested itself in litigation against pharmacy benefit managers. The apparent goal of a Pharmacy Benefits Manager (PBM) is to deliver cost efficiencies to health and welfare plans and employers through group purchasing power.[34] In the early 1990s, PBMs were "unheard of,"[35] but by 2001 they were administering pharmacy benefits under contracts to health and welfare plans encompassing more than 120 million participants.[36] Ted Afield described the role of the PBM in a 2001 article published in the *Columbia Law School Business Law Review*, as follows:

> PBM's serve numerous functions, including the establishment and administration of a retail pharmacy network; computerized claims processing and drug utilization review; and the establishment of formularies, which essentially are lists of Food and Drug Administration (FDA) approved drugs that are available through the PBM.

> The consolidation of these functions enables PBM's to play a significant role in cost containment. For example, a PBM can negotiate rebates and other discounts from drug suppliers on behalf of its customers by offering the suppliers' drugs a place on its formulary.[37]

This role presents a number of complex problems. First, while the PBM's role is purportedly designed to deliver cost efficiencies, PBMs have become gatekeepers for the entry of drugs into specific markets and thus a potential impediment to the unfettered choice of consumers. This may make a difference where drugs designed to deliver the same benefit, e.g., lower cholesterol, may pose different risks to the patient. For example, Lipitor, Baycol, and Crestor are all cholesterol lowering drugs but each comes with different risks. Not only are the risks different but they may vary depending on the unique health history and characteristics of the patient. These three drugs are clearly not interchangeable absent informed decision-making by the plan participant. While Crestor is currently on the formulary of at least one large PBM, it is also on the "do not use" list of the Washington, D.C., public interest group, Public Citizen, which has concerns about its impact on renal function. Baycol, which at one time was a competitor of Lipitor, was the subject of a recall in 2001.

Even where the risks of the drug are equivalent, pharmaceuticals designed to address the same illness or prophylactic purpose may have different delivery devices which govern how and where (i.e., in what part of the body) the drug dissolves. This makes a difference in how long the drug will stay in the body. A drug with a coating that allows it dissolve in the small intestine will generally stay in the body longer than a drug with a coating that allows for the drug to dissolve in the stomach.[38]

In sum, choosing the right drug is an important decision and one that should be based on the therapeutic needs of an individual patient. To the extent that a PBM curtails the ability of a patient to make the choice, its conduct negatively impacts patient care.[39]

Second, and to compound the problem, the PBM's choice of what to list on its formulary is undoubtedly influenced by what rebate it may get from the manufacturer. In many cases, these rebates are not immediately known to health plan trustees. Nor are they readily apparent to plan participants who are directed to use the drugs listed in the PBM's formulary.

Third, the potential for conflict is increased where the PBM is owned by or tied to a drug manufacturer. In 2004, the United States District Court for the Southern District of New York approved a $42.5 million dollar settlement involving pharmacy benefit manager Medco Health Solutions.[40] In its Memorandum Opinion approving the settlement, the Court summarized the class members' claims as follows:

> Plaintiffs claim that Medco held itself out as an independent pharmacy benefits management company ("PBM") that could control the quickly rising costs of prescription drugs by aggregating the purchasing power of employee benefit plans and thereby negotiating favorable purchasing terms with drug manufacturers. In reliance on Medco's promise of cost containment, Plan sponsors entrusted Medco with discretionary authority over certain aspects of the management of their pharmacy benefit plans ("Plans") for the primary purpose of cost containment. Plaintiffs claim that Medco "systematically misused its fiduciary authority, and its management of formularies and drug-switching programs, among other purposes (i) to increase the market share in specific drugs of its parent company Merck, and (ii) to divert rebates from drug manufacturers to itself, both at the expense of the plans. Plaintiffs contend that Medco did not disclose the nature of its plan management practices of the extent to which the plans failed to obtain benefits, or incurred costs, because of such practices.

On the initial appeal, the settlement was rejected, but was approved after remand. On December 8, 2005, the United States Court of Appeals for the Second Circuit in *Central States Southeast and Southwest Area Health and Welfare Fund v. Merck-Medco Managed Care*, 433 F.3d 181 (2d Cir. 2005), vacated and remanded the settlement after determining that the record did not demonstrate that the Plaintiffs had met the United States Constitution Article III standing requirements. On remand, Plaintiffs submitted information to the District Court pertaining to their injuries and the District Court entered a finding that, in fact, the Plaintiffs were injured as a result of the Defendant's conduct. In 2007, on appeal after the remand, the Second Circuit approved the settlement after it found sufficient evidence that one of the Plaintiffs was "involved in a contractual relationship with Medco so as to give her standing."[41]

Third-party payors have also effectively used the antitrust laws to target industry practices that foreclose competition and maintain high prices for prescription drugs. Federal and State antitrust and consumer protection laws bar schemes to monopolize, fix prices, or otherwise impede fair

competition. The Federal Trade Commission and the attorney generals of multiple states have historically pursued the drug industry for violations of consumer and antitrust laws.[42]

While federal antitrust laws generally restrict the ability of those who can bring suit to consumers who were direct purchasers, litigation by health and welfare funds under state antirust laws that allow for "indirect purchaser" litigation has proven to be a viable avenue for recovery. A number of states including Illinois and Tennessee have statutes that protect the rights of "indirect purchasers" who have been victimized by anticompetitive conduct.

Acting in concert and/or with the aid of PBMs, or other middlemen, the drug industry has been a hotbed for anticompetitive activity, driving up costs for consumers including health and welfare funds.

One scheme has involved efforts to inflate the "average wholesale price" ("AWP") of drugs so as to provide prescribing physicians an unlawful kickback where they are administering drugs covered by Medicare Part B.

While Medicare does not generally cover the cost of prescription drugs that a patient administers to himself, it does cover approximately 450 outpatient drugs, including ones that are administered by a doctor, and certain self-administered outpatient drugs. Through the Medicare Part B program, the federal government reimburses health care providers, such as physicians, for up to 80 percent of the allowable costs of certain prescription drugs that they administer directly to patients. The remaining 20 percent is paid for by the Medicare Part B beneficiary or her/his health and welfare fund, if it covers the drug.

Table 1. FCA Drug Settlements Following Government Intervention

Company	Allegations	Settlement Date	Total Settlement Amount	Criminal Fine + Disgorgement of Profits	Civil Settlement
Pfizer	Off-label marketing of Geodon, Bextra, Zyvox and Lyrica; kickbacks to doctors	September 2009	$2.3 billion	$1.3 billion	$1 billion
Eli Lilly	Off-label marketing of antipsychotic drug Zyprexa	January 2009	$1.4 billion	$615 million	$800 million
Cephalon	Off-label marketing of Gabitril, Actiq and Provigil between 2001 and 2006	September 2008	$425 million	$50 million	$375 million
Bristol-Myers Squibb	Illegal kickbacks to doctors, pharmacies and wholesale customers; price inflation on drugs including Serzone; off-label marketing of Abilify between 2002 and 2005	September 2007	$515 million	$25 million	$490 million
Cell Therapeutics	Off-label marketing of anti-cancer drug Trisenox between 2001 and 2005	April 2007	$10.5 million	None	$10.5 million
Intermune	Off-label marketing of Actimmune between August 2002 and January 2003	October 2006	$36.9 million	None; prosecution deferred based on cooperation with investigation	$30.2 million federal; $6.7 million to states
Eli Lilly	Off-label marketing of Evista	December 2005	$36 million	$12 million	$24 million
Serono	Off-label marketing and kickbacks for AIDS drug Serostim	October 2005	$704 million	$136.9 million	$567 million
Warner-Lambert	Off-label marketing of Neurontin between 1994 and 2002	May 2004	$430 million	$240 million	$190 million

Medicare uses the AWP as set by the industry through a "Red Book" to establish a reimbursement rate. In *In Re Pharmaceutical Industry Average Wholesale Price Litigation*,[43] the Plaintiffs alleged that the industry reported inflated wholesale prices (in the Red Book) which had the impact of setting Medicare reimbursement rates higher than the proper cost. In the case of Abbott Pharmaceutical's drug, Acyclovir, Abbott reported an AWP of $1,047.38 when the actual AWP, according to the Plaintiffs, should have been $349.05. This "spread" provided a windfall to "providers" who were incentivized to give the drug. Unfortunately, it caused funds to pay a co-pay of almost 60 percent of the AWP as opposed to the proper 20 percent.

Other schemes which have increased costs to consumers have included efforts by companies to impede market entry by generic competitors once a patent has expired. These efforts, sometimes unlawful, have involved combinations of activities including sham regulatory actions which have the effect of delaying generic drug approval or the execution of agreements with PBMs that impede generic entry into the marketplace. Through agreements with PBMs, companies can provide the PBM with a hefty rebate in exchange for exclusivity or near exclusivity on the PBM's formulary.

Overall, antitrust actions over recent years have involved a wide range of drugs including Procardia XL, Coumadin, Buspar, Taxol, Tiazac, Adalat and Lorazepam to name a few.

Historically, the third-party payors have relied on the FDA and the

medical community to insure that drugs were safe and that they were used in an appropriate way. A wave of problematic drugs including the Cox-2 inhibitors Vioxx, Bextra and Celebrex have caused private third-party payors, including insurance carriers, to rethink this reliance. In the United States third-party payors have initiated class action litigation over drugs from the cholesterol drug, Vytorin,[44] to anti-psychotics including Seroquel and Risperdal.

Federal and State Third-Party Payors: The False Claims Act

One of the more unique challenges to industry marketing practices has come under Federal and State False Claims Acts.[45]

First passed by Congress during the Administration of President Abraham Lincoln, the False Claims Act has provided private citizens with the means to step into the shoes of the United States Government and seek redress against contractors that have defrauded the government. In 1986, the law was amended to provide private citizens the right to prosecute cases against wrongdoers – in the name of the government – even where the government, through the United States Department of Justice, has declined to step into the case (i.e., "intervene") itself.

The federal False Claims Act, which applies to the recovery of federal dollars, provides that:

> Any person who –
>
> (A) knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval;
>
> (B) knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim. . .is liable to the United States Government for a civil penalty of not less than $5,000 and not more than $10,000. . .plus 3 times the amount of damages which the Government sustains because of the act of that person.

The term "claim" is generally defined broadly to include any request or demand for money or property when a portion of that money or property has come from the Government.[46]

While there are certain limitations on who has standing to bring a suit, in general a suit cannot be based on "public information," as that term is defined in the statute, and it cannot be brought based on "allegations or transactions which are the subject of a civil suit or an administrative civil money penalty proceeding in which the Government is already a party."[47]

Courts have held that a manufacturer's off-label marketing of drugs and/or kickbacks used to induce the writing of prescriptions causes doctors to write prescriptions that are reimbursed by the Medicaid and Medicare systems (state and federal dollars) thereby "causing" false claims to be filed.

In *U.S. ex rel. Franklin v. Parke-Davis*, 147 F. Supp.2d 49 (D. Mass. 2001), a whistleblower, David Franklin, filed suit under False Claims Act against his former employer, Parke-Davis. Franklin had direct knowledge of the company's marketing practices of the drug Neurontin, and he alleged that the company's off-label marketing and kickbacks paid to doctors – to induce prescription writing -- resulted in the filing of false claims for payment and approval. Specifically, Franklin accused Parke-Davis of illegal marketing practices, including the off-label promotion of its anticonvulsant medication, Neurontin. The drug had only been approved for use in patients with epilepsy, but in 2001 over 80% of its $1.8 billion in sales were for indications unapproved by the FDA. In 2004, Pfizer – which had by that time purchased Parke-Davis – acknowledged that Parke-Davis had aggressively marketed Neurontin by illicit means for unrelated conditions including bipolar disorder, pain, migraine headaches, and drug and alcohol withdrawal, and consented to $430 million in damages to resolve the litigation.

Among his allegations, Franklin claimed that Parke-Davis' medical liaisons – of which he was one – were instructed to make exaggerated or false representations concerning the safety and efficacy of the company's drugs and to off-label market the drugs for uses and in dosages that were outside the indication, i.e., off-label.

Franklin further alleged that because kickbacks, employed to encourage usage of a product paid for by the Medicare system, are illegal,[48] Parke-Davis had violated the FCA. Franklin's theory was premised on the argument that kickbacks alone were a predicate to an FCA violation. Franklin alleged that Parke-Davis disguised its kickbacks in the form of payments to doctors for sham consulting arrangements, participation in "speakers bureaus," or as arrangements to conduct studies. Sustaining Franklin's causes of action (asserted on behalf of the Government) the court explained that in some cases "the FCA can be used to create liability where failure to abide by rule or regulation amounts to a material misrepresentation made to obtain a Government benefit."[49] In this case, Parke-Davis was alleged to have engaged in a wrongful pattern of conduct which caused the prescriptions to be written – based on false information – which in turn were reimbursed by government health care plans.

Subsequent to the *Franklin* case, the federal and state governments have intervened and settled in a number of cases filed by private whistleblowers, as shown in Table 1.

The largest of these settlements involved the September 2009, $2.3 billion dollar settlement entered into by the United States Government and various state governments with Pfizer, Inc. That settlement was the result of litigation under the False Claims Act initiated by six lead whistleblowers and at least 10 other whistleblowers who had filed cases that post dated the filings of the initial six.

Glenn Demott, a onetime Pfizer sales representative, was one of those whistleblowers. As a Pfizer employee, Demott had been one of the company's most successful representatives. He had earned numerous regional and national sales awards and had risen to the position of senior sales consultant. Notwithstanding his success at Pfizer, Demott had serious concerns about the way in which he was being asked to market the company's drugs.

After failing to get his concerns addressed by Pfizer, in the fall of 2005, Demott filed a complaint in the United States District Court in Boston, Massachusetts. As is required by the FCA, his cause of action was filed under seal meaning that it was kept secret from Pfizer but given to government prosecutors. The FCA seal allows the government –through the Department of Justice and state attorneys general – to conduct an investigation before the company knows that it is the suspect of wrongdoing.

Prior to filing his case, Demott had disclosed his concerns to the United States Department of Justice and the Inspector General for the United States Department of Health and Human Services (HHS) which oversees the Medicare program. He also made disclosures to various state attorney generals. His disclosure provided an outline of the facts, a listing of potential witnesses, and binders of documents supporting his claims. This disclosure--along with disclosures made by other whistleblowers – was sufficient to prompt the government to begin a four-year investigation. Through his initial complaint and an amended filing, Demott made the following claims with regard to the following Pfizer products which were laid out in paragraphs 10-16 of his Amended Complaint and Jury Demand:

BEXTRA

10. Pfizer waged an illegal "off-label" marketing campaign to promote the prescription drug Bextra for non-FDA approved uses. The FDA approved Bextra for treatment of rheumatoid arthritis, osteoarthritis, and primary dysmenorrhea (a type of menstrual pain). Rather than awaiting FDA approval for the drug's alternate uses, Pfizer chose to promote such off-label uses of Bextra as providing acute, dental, podiatric, pre-operative and postoperative pain relief, despite Pfizer's awareness of the FDA's prohibition on off-label marketing. Pfizer's fraudulent marketing scheme also involved promotion of unproven claims of superior speed of onset, superior efficacy and superior gastrointestinal safety. To do so, Pfizer misrepresented and falsified data from research studies, made false certifications of physician Medical and Drug Information requests, and used unreliable, misleading and irrelevant data to promote its claims of superior efficacy and cardiovascular and gastrointestinal safety and urge higher dosing than the FDA approved.

CELEBREX

11. Pfizer actively promoted Celebrex, its COX-2 inhibitor, "off-label" to increase its sales of that drug. Celecoxib is a non-steroidal anti-inflammatory COX-2 inhibitor manufactured and marketed by Pfizer under the brand name "Celebrex." The FDA approved Celebrex on December 31, 1998 for the treatment of pain and inflammation associated with adult rheumatoid arthritis and osteoarthritis. The FDA expanded Celebrex's approved uses after the initial approval, but never generally expanded it for all types of pain or inflammation. Additional later approvals were for Familial Adenomatous Polyposis (FAP); for management and treatment of primary dysmenorrhea (a type of menstrual pain); for juvenile rheumatoid arthritis; for ankylosing spondylitis; and for acute pain in adults arising from dental or orthopedic surgery.

12. Pfizer promoted Celebrex as having superior efficacy, superior gastrointestinal safety, and superior cardiovascular and cardio-renal safety. These false claims of Celebrex's properties diminished the safety warning sections of the package insert and caused physicians to expand their use of Celebrex to patients who would not otherwise have received the drug because of the patient's risk factors.

LYRICA

13. Pfizer sales representatives marketed Lyrica for off-label uses, including for pain, in advance of its approval by the FDA and thereafter. Pfizer's agents falsified physician requests for medical information

concerning Pfizer's prescription drug Lyrica before that drug had been approved for any uses by the FDA. When the Relator reported this conduct to Pfizer's Compliance Department, Pfizer took no action against the sales representatives, in violation of the terms of its Corporate Integrity Agreement.

RELPAX

14. Pfizer routinely paid improper kickbacks to physicians in order to induce those physicians to prescribe Pfizer's migraine prescription drug Relpax and engaged in other unlawful marketing practices to increase Relpax sales. These kickback schemes violated 42 U.S.C. § 1320a-7b(b) (the "'Medicare Fraud & Abuse/Anti-Kickback Statute") and caused false or fraudulent claims for Pfizer's drugs to be filed by physicians and medical institutions for reimbursement from Federal and State government-funded health programs. Pfizer misrepresented the results of scientific studies to promote Relpax over competitors' migraine medication and illegally used information from the studies to promote Relpax, including promoting dosages that were higher than the FDA had approved.

DEPO-PROVERA

15. For years, Pharmacia, Pfizer's predecessor, trained and encouraged its district managers and sales representatives to "'do deals" and "'barter" with physicians and medical institutions by offering large quantities of drug samples (what Pfizer now calls "starters") in exchange for large or standing orders from the physicians and medical institutions for those or other drugs. This became an accepted practice that later resulted in Pfizer-trained District Managers and sales representatives exchanging large numbers of Pfizer-supplied Depo-Provera (an injectable contraceptive) samples (up to 100) in return for the physicians and medical institutions placing larger Depo-Provera orders. To accomplish this, Pfizer sales representatives first promised physicians free sample doses of DepoProvera, an injectable contraceptive, in exchange for the physicians purchasing Estring (FDA approved for treating various post-menopausal conditions). This bartering continued thereafter, without Estring, which illegally manipulated Medicaid "best price" and "average manufacturer price" reimbursement and rebate calculations. The deals drastically decreased the average wholesale price per dose paid and reimbursed the physicians at an artificially higher rate. This practice also improperly influenced physicians' decisions about whether to prescribe Depo-Provera, so that patients receiving those drugs could not be certain that their treatment was guided solely by their physicians' independent medical assessment of their diagnoses.

GEODON

16. Pfizer marketed its atypical antipsychotic drug, Geodon (ziprasidone hydrochloride), initially indicated for the treatment of schizophrenia, to a high-volume Medicaid clinic called Townstreet Medical Clinic, located in Columbus, Ohio. Pfizer aggressively promoted Geodon to this practice, which served a large Medicaid patient population, despite the fact that Pfizer was aware of a dangerous side effect caused by the drug. In particular, Geodon could create serious, potentially fatal heartbeat irregularities. Pfizer engaged in a pattern of reckless marketing of Geodon, while knowing that Geodon was being used off-label for conditions other than its approved uses. In addition to this aggressive marketing for non-indicated purposes, Pfizer paid kickbacks to the Townstreet Clinic through the payment of grants and "preceptorships." Defendant continued to aggressively market to the Townstreet Clinic physicians even after the prescriptions were known to be inappropriate and fraudulent.

The gravamen of Demott's claims on behalf of the government were that Pfizer's unlawful marketing practices caused government third-party payors to spend money that they otherwise would not have spent. After an investigation involving countless documents and witness interviews the Government announced in July 2009 that it had reached a settlement with Pfizer. For their efforts in prompting the Government investigation that lead to the recovery, each of the Relators was provided a share (i.e., a "bounty") of the Government's recovery.

In addition to the civil prosecution of Pfizer for monetary damages under the FCA, the Government also prosecuted the company for criminal wrongdoing. As a result, a Pfizer subsidiary agreed to plead guilty to criminal conduct.

The civil and criminal prosecutions resulted in three important documents: (1) a settlement agreement of the False Claims Act violations, (2) a criminal plea, and (3) a Corporate Integrity Agreement (CII) with the Department

of Health and Human Services which governed the company's conduct going forward.

All told, the FCA settlement agreement covered wrongful conduct in the marketing of the drugs Bextra, Geodon, Zyvox, Lyrica, Aricept, Celebrex, Lipitor, Norvasc, Relpax, Viagra, Zithromax, Zoloft and Zyrtex. The settlement laid out the claims that the government could have asserted had it pursued the case through trial:

> (1) Bextra: During the period February 1, 2002, through April 30, 2005, Pfizer: (a) illegally promoted the sale and use of Bextra for a variety of conditions (including acute pain and various types of surgical pain) and at dosages other than those for which its use was approved by the Food and Drug Administration ("FDA") (i.e., "off label" uses), in violation of the FDCA, 21 U.S.C. § 331, et seq., and which were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Bextra; (b) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Bextra, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b); and (c) made and/or disseminated unsubstantiated and/or false representations or statements about the safety and efficacy of Bextra. As a result of the foregoing conduct, Pfizer knowingly caused false or fraudulent claims for Bextra to be submitted to, or caused purchases by, Medicaid and the other Federal Health Care Programs.

(2) Geodon: During the period from January 1, 2001, through December 31, 2007, Pfizer: (a) illegally promoted the sale and use of Geodon for a variety of off-label conditions (including depression, bipolar maintenance, mood disorder, anxiety, aggression, dementia, attention deficit hyperactivity disorder, obsessive compulsive disorder, autism and posttraumatic stress disorder), and for patients (including pediatric and adolescent patients) and dosages that were off-label, in violation of the FDCA, 21 U.S.C. § 331, et seq., and which were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Geodon; (b) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Geodon, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b); and (c) made and/or disseminated unsubstantiated and/or false representations or statements about the safety and efficacy of Geodon. As a result of the foregoing conduct, Pfizer knowingly caused false or fraudulent claims for Geodon to be submitted to, or caused purchases by, Medicaid, Medicare and the other Federal Health Care Programs.

(3) Zyvox: During the period January 1, 2001, through February 28, 2008, Pfizer: (a) illegally promoted the sale and use of Zyvox for a variety of off-label conditions (including infections caused by methicillin-resistant Staphylococcus aureus ("MRSA") generally, rather than only those types of MRSA infections for which Zyvox was FDA-approved), in violation of the FDCA, 21 U.S.C. § 331, et sec., and which were not medically accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Zyvox; (b) made and/or disseminated unsubstantiated and/or false representations or statements about the safety and efficacy of Zyvox (including that Zyvox was superior to vancomycin, its primary competitor drug for these indications); and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Zyvox, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320-7b(b). As a result of the foregoing conduct, Pfizer knowingly caused false or fraudulent claims for Zyvox to be submitted to, or caused purchases by, Medicaid, Medicare and the other Federal Health Care Programs.

(4) Lyrica: During the period September 1, 2005, through October 31, 2008, Pfizer: (a) illegally promoted the sale and use of Lyrica for a variety of off-label conditions (including chronic pain, neuropathic pain, perioperative pain, and migraine), in violation of the FDCA, 21 U.S.C. § 331, et seq., and which were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Lyrica; (b) made and/or disseminated unsubstantiated and/or false representations or statements about the safety and efficacy of Lyrica, including claims that it was superior to Neurontin and its generic equivalent, gabapentin;

and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Lyrica, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320-7b(b). As a result of the foregoing conduct, Pfizer knowingly caused false or fraudulent claims for Lyrica to be submitted to, or caused purchases by, Medicaid, Medicare and the other Federal Health Care Programs.

(5) Kickbacks: From January 2001, through December 2004, Pfizer paid illegal remuneration for speaker programs, mentorships, preceptorships, journal clubs, and gifts (including entertainment, cash, travel and meals) to health care professionals to induce them to promote and prescribe the drugs Aricept, Celebrex, Lipitor, Norvasc, Relpax, Viagra, Zithromax,Zoloft, and Zyrtec, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b). As a result of the foregoing conduct, Pfizer caused false claims to be submitted to Medicaid and TRICARE.

The CII, yet a separate document, outlined how the company would monitor its conduct going forward, the requirement that the company disclose payments made to doctors, and a requirement that doctors be informed of the settlement. The criminal plea, taken by a Pfizer subsidiary, involved criminal conduct in the marketing of Bextra only.

Shareholders

Some of the underlying facts that gave rise to the FCA action against Pfizer have also given rise to an action brought by shareholders of Pfizer under U.S. securities laws. In a case brought in the United States District Court for the Southern District of New York, institutional investors in Pfizer – including the Teachers Retirement System of Louisiana – have alleged that misrepresentations regarding the safety and efficacy of Bextra and Celebrex fraudulently impacted the price of Pfizer stock. When the market learned of problems related to these drugs, the stock price dropped, causing injury to a class shareholders that purchased the stock while the company was making the misrepresentations or fraudulent omissions. While the Plaintiffs have filed a 142-page complaint against Pfizer, the claims are summarized in paragraphs 2-9, as follows:

2. For more than five years, Pfizer misrepresented Celebrex as a risk-free painkiller, safer than aspirin, ibuprofen and other drugs, which could be taken by almost anyone for a number of types of chronic pain. Pfizer also misrepresented Bextra as a safe painkiller for a wide variety of applications. Unbeknownst to investors, however, from at least as early as 1999, Pfizer had in its possession data regarding serious cardiovascular risks of Celebrex and/or Bextra that contradicted or rendered false statements made by the Defendants throughout the Class Period about the alleged safety of those drugs. Once the truth – which was known by Pfizer for years – was revealed, sales of Celebrex fell dramatically and Bextra was removed from the market. As a result, Pfizer's stock price declined precipitously.

3. It is now clear that Pfizer and its senior management knew that from its initial approval, Celebrex should have been the subject of the "black box" FDA warning it now carries regarding the substantial risk of cardiovascular harm that can be caused by using the drug. Had this "black-box" warning been included on Celebrex's label, it never would have been more than what it is now -- a niche painkiller used by a segment of special-need patients. Further, the Defendants knew or were reckless in not knowing that Bextra, because of its extraordinary dangers to users, never even should have been approved for use by consumers.

4. The Defendants failed to disseminate to the public results from a study ending in 1999, that found patients taking Celebrex to treat mild Alzheimer's disease had a statistically significant increase in heart attacks and other cardiovascular side effects (the "1999 Study"). The Defendants failed to publicly disclose that the 1999 Study showed Celebrex increased by nearly four times the risk of cardiovascular problems compared with a placebo. Dr. Lon S. Schneider, a professor of psychiatry, neurology, and gerontology at the University of Southern California Keck School of Medicine in Los Angeles, who was part of the safety monitoring board for Celebrex, said, regarding the 1999 Study: ***"It should have been fully published in 2000, and perhaps if it had been some attention might have been drawn to potential safety issues."*** (Emphasis added). Similarly, Dr. Kenneth Brandt, a professor of medicine at Indiana University School of Medicine, who was part of a panel that reviewed Celebrex safety in 2001, said that, had the panel known about the study, the group would have recommended that both Vioxx and Celebrex be taken with greater caution. That panel decided in 2001 that Vioxx,

but not Celebrex, should carry a warning about its cardiovascular risks. That difference is one of the main reasons Celebrex had greater sales than Vioxx.

5. Moreover, it is clear that the information about the safety of Celebrex that was hidden from those outside of Pfizer, was well-known inside the company. According to one of the inventors of Celebrex and Bextra, members of senior management were well aware of the clinical studies that were conducted on Celebrex and Bextra. Statements by former employees of Pharmacia Corporation ("Pharmacia") (now Pfizer) who worked on the development of Celebrex, confirm that all of the negative effects and problems were reported to top management.

6. It was not until December 17, 2004, when the National Cancer Institute announced the premature cessation of a trial of Celebrex because of a dramatic increase in cardiovascular death and stroke among the participants of the trial that the truth began to emerge concerning Celebrex's safety. Thereafter, on January 31, 2005, Pfizer acknowledged that the previously undisclosed 1999 Study, conducted prior to Celebrex being approved by the FDA, found that elderly patients taking the drug were far more likely to suffer heart problems than patients taking a placebo. Not only was the study concealed from the investing public for five years, but Pfizer withheld it from the FDA during the FDA's 2000-01 review of the efficacy and safety of Celebrex. Similarly, only in October 2004, following the very public controversy over Vioxx, did Pfizer disclose information regarding a study of Bextra that showed serious cardiovascular problems associated with the use of that drug.

7. From the initial approval of Celebrex by the FDA in 1999, and the subsequent FDA approval of Bextra in 2001, through April 2005, Pfizer's website contained no warning about the cardiovascular dangers associated with the use of Celebrex and Bextra that it knew existed. Today, Bextra is no longer on the market and Pfizer's Celebrex website states: ***"Important Information: CELEBREX may increase the chance of a heart attack or stroke that can lead to death."*** (Emphasis added).

8. Sales of Celebrex were $2.6 billion in 2000 and $3.1 billion in 2001. After the introduction of Bextra, the joint sales of Celebrex and Bextra totaled $3.5 billion in 2002, approximately $3.4 billion in 2003, and $4.5 billion in 2004. The joint sales of Celebrex and Bextra constituted between 6% and 11% of Pfizer's total sales from 2002 to 2004.

9. Beginning with Pfizer's first announcement in October 2004, regarding Bextra, Pfizer's sales of the drugs began to decline. The effect of the black box warning label on Celebrex and the withdrawal of Bextra from the market caused a material decline in Pfizer's revenues and earnings. Revenues from Celebrex fell from $2.294 billion for the first nine months of 2004 to $1.258 billion for the same period in 2005, a decline of 45%. Bextra's revenues for the first three quarters declined by more than $925 million from 2004 to 2005. Combined, Celebrex's and Bextra's revenues for the first nine months of 2005 fell by over $2 billion compared to the first nine months of 2004, a decline of 63%. As a result, Pfizer's common stock price fell dramatically. From October 18, 2004 to October 26, 2005, Pfizer's stock experienced a series of drops, falling from $29.00 per share on October 18, 2004 to $21.06 per share on October 26, 2005 (a decline of $7.94 per share or 27.4%), representing a loss in market capitalization of $58.5 billion.

On February 28, 2008, the court granted the Defendants' motion to dismiss. Pfizer's knowledge that evidence of torcetrapib's efficacy was inconclusive and did not support an inference that its optimistic statements were materially misleading, the judge ruled. While the Pfizer securities litigation did not reach a jury, by allowing the case to go through the discovery phase of the judicial process opened Pfizer's conduct to public scrutiny and oversight.

Conclusion

In the United States, regulation of the pharmaceutical industry is subject to formal and informal control. Laws, regulations, and oversight by Congress and stakeholders has been the means by which the industry has been tested as to the safety and efficacy of its products. The system is imperfect and involves a fluid interrelationship of all of the competing pressures, including the desire for breakthrough drugs and scientific innovation balanced against the health and safety of consumers. It is a system that has brought a diverse array of stakeholders together.

ENDNOTES

[1] Originally publication in the *Public Interest Law Journal,* Peking University Beijing, People's Republic of China. The Peking University Public Interest Law program is a program in cooperation with the China Law Center, Yale Law School.

[2] Reuben A. Guttman is a Partner with the New York based law firm of Grant & Eisenhofer. Mr. Guttman practices in the firm's Washington, D.C. office. Mr. Guttman heads the firm's False Claims Act practice which involves complex pharmaceutical industry fraud and was counsel for one of the six prime "relators" in litigation resulting in the United States Government's recovery of $2.3 billion from Pfizer, Inc. He is a member of the national faculty of the Emory University Kessler-Edison Trial Advocacy Program and he has been a faculty member of the National Institute for Trial Advocacy. The author credits Bradley Hillis, an attorney with Grant & Eisenhofer, for his review of and contributions to this paper.

[3] There is a financial benefit from FDA approval of a drug and, as an economic calculation, the value of the "stamp of approval," expressed in a company's stock price, exceeds the procedural costs, according to some commentators. Ariel Katz, Pharmaceutical Lemons: Innovation and Regulation in the Drug Industry, 14 Mich. Telecomm. & Tech. L. Rev. 1 (2007) ("Although intuitively appealing, the argument that drug regulation negatively affects the incentives to innovate does not fully capture the role that regulation plays in this industry. [T]he regulatory framework is not solely a burden imposed on the industry; it also provides a valuable service to the industry. Specifically, drug regulation provides certification of drug quality.")

[4] Employee Retirement Income Security Act ("ERISA") § 404(c); 29 U.S.C. § 1104(c) (1974).

[5]Food, Drug & Cosmetics Act ("FDCA"), 21 U.S.C. § 301 *et seq.* (1938). The FDCA's precursor law, the Pure Food and Drug Act of June 30, 1906, P.L. 59-384, 34 Stat. 768, was part of President Theodore Roosevelt's progressive platform, and was inspired by Upton Sinclair's vivid descriptions of Chicago's meatpacking factories in his 1906 novel, *The Jungle*. The Pure Food and Drug Act of 1906 also required that so-called "patent medicines," which had previously been sold with secret ingredients or misleading labels, be accurately labeled with contents and dosage. While the 1906 law required disclosure of ingredients, it had a limited ability to regulate safety. The limits of the 1906 were tested before the U.S. Supreme Court in *United States v. Forty Barrels and Twenty Kegs of Coca-Cola*, 241 U.S. 265 (1916), in which the government sought to reduce the amount of caffeine in the popular soda pop. The Supreme Court ruled the law did not grant the government the power to regulate the amount of caffeine, so long as the ingredient was disclosed on the label. The company later settled with the government and curbed the amount of caffeine. The Pure Food and Drug Act of 1906 was largely replaced by the much more comprehensive Food, Drug, and Cosmetic Act of 1938, passed under Teddy Roosevelt's cousin, President Franklin D. Roosevelt.

[6] *Wyeth v. Levine* , 555 U.S. ___, 129 S.Ct. 1187, 1202 (2009).

[7] In contrast, there are some agencies established by Congress that only make decisions through adjudications. For example, the National Labor Relations Board (NLRB), which regulates the relationship between workers engaging in union activity, i.e., protected-concerted conduct, and their employers, establishes its rules of the workplace by holding hearings concerning specific labor disputes and publishing decisions about how the National Labor Relations Act (NLRA), promulgated by Congress, should be applied. *See, e.g.,* 29 U.S.C § 155, *et seq.*

[8] *See*, 21 U.S.C. § 331(d), § 355(a).

[9] Once the monopoly period granted by the drug's patent has expired, other manufacturers may produce a "generic" version of the drug. A simplified application is allowed for the generic version of drug, given the rigorous testing of the original version. The Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Act") established a new process for generic drugs to enter the market, the Abbreviated New Drug Application ("ANDA"). Congress intended the Act to "make available more low-cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." Adam R. Young, Generic Pharmaceutical Regulation in the United States With Comparison to Europe: Innovation and Competition, 8 Wash. U. Global Stud. L. Rev. 165, 169, n.30 (2009).

[10] *See*, 21 U.S.C. § 331(a)-(b), § 352(a),(f).

[11] *See*, 21 U.S.C. § 301.

[12] The issue of whether conflicts of interest have tainted studies used to secure FDA approval of drugs is indeed serious. Dr. Marcia Angell, a former editor of one of the more prominent medical publications in the United States, noted in her article, "Drug Companies & Doctors: A Story of Corruption," *N.Y. Review of Books* 56:1 (Jan. 15, 2009), that "[i]t is simply no longer possible to believe much of clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion which I have reached slowly and reluctantly over my two decades as an Editor of the *New England Journal of Medicine*."

[13] *See* Letter from Sen. Charles E. Grassley to James A. Wagner, Ph.D., Emory University, September 16, 2008.

[14] Gardiner Harris, "Heart Surgery Drug Pulled From Market," *N.Y. Times*, November 6, 2007.

[15] *Wyeth v. Levine*, 555 U.S. ___, 129 S.Ct. 1187 (2009).

[16] Subsequently, on October 15, 2009, Wyeth was acquired by Pfizer, Inc.

[17] An arguably safer method of administration is to introduce the drug through a saline solution in a hanging drip bag, according to medical testimony at trial. *Wyeth v. Levine*, *supra*, Respondent's Brief in Opposition, at 4.

[18] *Wyeth*, 129 S.Ct. at 1191.

[19] *Id*.

[20] Wyeth's argument was based on the doctrine of pre-emption, which arises from

the Supremacy Clause of the United States Constitution, Article VI, Clause 2. That clause establishes the Constitution, Federal Statutes, and U.S. Treaties as the "supreme law of the land." *Wyeth*, 129 S.Ct. at 1195.

[20] *Wyeth*, 129 S.Ct. at 1194.

[21] The Solicitor General of the United States represented the position of the FDA before the United States Supreme Court.

[22] *Wyeth*, 129 S.Ct. at 1201.

[23] *Id.*, at 1202.

[24] Securities actions are brought by shareholders against a company and its directors and derivative actions are brought by shareholders in the name of the company against those – including officers and directors – who have injured the company.

[25] Justice Louis D. Brandeis wrote: "Sunshine is said to be the best of disinfectants." Brandeis, L.D., *Other People's Money and How the Bankers Use It*, Melvin I. Urofsky, ed. (orig. 1914, reprint Bedford/St. Martin's: 1995), at 92.

[26] *Ashcroft v. Iqbal*, 129 S.Ct. 1937, 1949 (2009).

[27] The phrase "ask your doctor" or a similar phrase appears in almost all direct to consumer television advertisements. *Compare*, Mintzes, B., Morgan, S. & Wright, J.M., "Twelve Years' Experience with Direct-to-Consumer Advertising of Prescription Drugs in Canada: A Cautionary Tale," PLoS ONE. 2009; 4(5): e5699 (In Canada, researchers have found that: "The suggestion to 'ask your doctor' is no guarantee that the [TV] viewer is protected, as doctors often prescribe medicines that patients request although they might not have otherwise chosen to do so.").

[28] *See*, *Sierra Club v. Morton*, 405 U.S. 727 (1972); compare *Fair Housing Council of Suburban Philadelphia v. Montgomery Newspapers*, 141 F.3d 71, 78 (3d Cir.1998), where no standing was found as no member of the plaintiff group had sustained injury in fact. The concept of constitutional standing is particular to federal courts, i.e., courts created by Article III of the U.S. Constitution. Standing requirements in state court may differ from state to state.

[29] The group publishes its findings at its website,www.worstpills.org.

[31] *U.S. ex rel. Franklin v. Parke Davis*, 210 F.R.D.257, 260 (D. Mass 2002), *citing Public Citizen v. Liggett Group, Inc.*, 858 F.2d 775, 780 (1st Cir. 1988).

[32] China has similar gaps in its system as the government pays some portion of the cost of treating illness but not all costs. In contrast, countries including Great Britain and Israel have been able to implement universal coverage for all citizens.

[33] ERISA § 404(c); 29 U.S.C. § 1104(c) (1974).

[34] *See*, Afield, W.E., Note: The New Drug Buyer: The Changing Definition of the Consumer for Antitrust Enforcement in the Pharmaceutical Industry, 2001 Colum. Bus. L. Rev. 203.

[35] *Id*., at 210.

[36] *Id*.

[37] *Id.*

[38] An "enteric coating" is put on a pill to so that it does not dissolve until it reaches the small intestine. These coatings work because they do not dissolve in the acidic juices of the stomach. Enteric coatings are also used where the drug would irritate the stomach if it was dissolved in that organ.

[39] In a recent television news interview, for example, one PBM official indicated that Lipitor had been removed from his firm's "formulary" in favor of several generic brands and Crestor.

[40] *See, In Re: Medco Health Solutions, Inc. Pharmacy Benefit Manager Litigation*, 2004 U.S. Dist. LEXIS 28606, 2004 WL 1243873 (S.D.N.Y. May 24, 2004)(No. CLB, 03-MDL-1508).

[41] *Central States Southeast and Southwest Area Health and Welfare Fund v. Merck-Medco Managed Care*, 504 F.3d 229, 243 (2d Cir. 2007).

[42] *See, e.g.*, the February 5, 2002 press release from Tennessee Attorney General Paul G. Summers announcing the state's participation in the settlement of a price fixing case involving the drug Lorazepam (Mylan Pharmaceuticals); the April 27, 2001 press release from Texas Attorney General John Cornyn regarding his state's participation in an antitrust settlement against Mylan over ingredients to Lorazepam; the website of California Attorney General Bill Lockyer which documents antitrust actions and/or settlements involving contact lenses (Johnson & Johnson), the anti-cancer drug Taxol (Bristol-Myers Squibb), and the heart medication Cardizem (Aventis and Andrx Corporation).

[43] M.D.L. No. 1456, No. 01-cv-12257-PBS (D. Mass.).

[44] On August 5, 2009, third-party payors reached a $40 million settlement with Merck-Schering Plough over the company's failure to fully disclose information about the safety and efficacy of its drug, Vytorin. The TPP's alleged that had full information been made available to the medical community, fewer prescriptions would have been written. Schering-Plough Corp., Quarterly Report for Third Quarter ending September 30, 2009 (filed Oct. 29, 2009), SEC Form 10-Q, at 22.

[45] The Federal False Claims Act can be found at 31 U.S.C § 3729, *et seq*. There are 23 States and the District of Columbia that have promulgated their own False Claims Acts which allow citizens to bring suit to recover dollars that have been defrauded from the states. One of the most comprehensive websites which explains these laws is www.whistleblowerlaws.com.

[46] *See,* 31 U.S.C. § 3729(a)(2)(A).

[47] *See,* 31 U.S.C. § 3730(e)(3).

[48] *U.S. ex rel Franklin v. Parke-Davis*, 147 F. Supp.2d 39, 52 (D. Mass. 2001).

[49] *Id.*

1201 N. Market Street
Wilmington, DE 19801

1920 L. Street, N.W., Suite 400
Washington, DC 20036

485 Lexington Avenue
New York, NY 10017

www.gelaw.com