
Comment

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These Statements Have Not Been Approved by the FDA: Improving the Postapproval Regulation of Prescription Drugs

All consumers of prescription drugs serve as guinea pigs for the pharmaceutical industry, for every new drug remains basically ‘experimental’ even after it has been approved for general use.”¹ Although this assessment of the regulatory environment for approved prescription drugs may seem harsh, the friends and family of the nearly 28,000 consumers who likely died as a result of the postapproval regulation of Vioxx²—or lack thereof—would probably tend to agree. But should the system be changed to prevent future breakdowns in the monitoring of drug safety? If so, what are the proper roles for state and federal governmental actors, namely state

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¹ Richard A. Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1, 20 (1973) (footnote omitted).

² *F.D.A. Releases Memo on Vioxx*, N.Y. TIMES, Nov. 3, 2004, at C8, available at <http://query.nytimes.com/gst/fullpage.html?res=9C01E5DF163CF930A35752C1A9629C8B63>.

attorneys general and federal agencies? The answers to these questions directly or indirectly impact the lives and health of all Americans.

Sales in the pharmaceutical industry are a direct result of the confidence of consumers and physicians in prescription drug regulation. The U.S. Food and Drug Administration (FDA) plays a crucial role in the prescription drug marketplace by ensuring that the trust shared by consumers and physicians is well founded.³ This public and professional trust in prescription drugs arises, in large part, from both groups' confidence in the effectiveness and integrity of the FDA when performing its two primary functions: drug approval and postapproval drug-safety monitoring.⁴

The FDA, however, faces increasing skepticism in the public arena regarding its ability to effectively regulate approved drugs that have entered the market. According to a recent study, over half of American adults believe the FDA does a fair or poor job ensuring the safety of new prescription drugs.⁵ The same study found that 61% of American adults thought the FDA's safeguarding function was the most important area on which the agency should focus its energy.⁶

The negative attitude toward the FDA's efforts may be attributed to some aspects of the structure and implementation of regulation policies. The structure of both postapproval surveillance of prescription drugs and the decision-making processes that utilize the information collected from that surveillance suffer from numerous inefficiencies that serve to undermine the FDA's safeguarding

³ Phil B. Fontanarosa et al., *Postmarketing Surveillance—Lack of Vigilance, Lack of Trust*, 292 JAMA 2647, 2647 (2004).

⁴ *Id.* The FDA's effort in these two areas leads to consumer and physician expectations that correctly prescribed drugs "generally will have beneficial effects and will not cause significant harm." *Id.*

⁵ See Harris Interactive, *Confidence in FDA Hits New Low, According to WJS.com/Harris Interactive Study*, WALL ST. J. ONLINE, Apr. 23, 2008, at 2, available at http://www.harrisinteractive.com/news/newsletters/wshealthnews/HS_WSJ_HealthCarePoll_2008_v07_i05.pdf. The survey found that 58% of people polled had negative views toward the FDA's performance of its safeguarding function. *Id.* These results differ markedly from those revealed in a survey conducted in 2004: 56% of the people polled in that survey had positive beliefs about the FDA when asked identical survey questions. *Id.* Over 50% of the subjects in the 2008 study answered negatively in response to questions about their opinions regarding the following major functions of the FDA: ensuring that new prescription drugs are promptly available to the public, safeguarding the safety of prescription drugs produced outside of the United States, and administering the recall of prescription drugs when safety issues occur. *Id.*

⁶ See *id.*

mission. One such inefficiency stems from the fact that pharmaceutical companies—and not the FDA—are largely responsible for conducting postapproval safety trials of prescription drugs.⁷ Although this responsibility alone arouses suspicion, the company sponsoring the clinical trial also controls the reporting of the resulting data.⁸ Until recently, a pharmaceutical company had an unprecedented ability to conceal the unfavorable results of these safety studies without the FDA knowing it was doing so.⁹ Because of the limited information the FDA receives from the sponsoring companies, the agency normally only has access to safety information from physicians and other professionals in the health care industry who voluntarily report adverse events caused by the use of a prescription drug.¹⁰ As discussed below, voluntary reporting is fraught with deficiencies in the collection and communication of adverse event information.

Even in the unusual situation where the FDA has accurate safety and efficacy information about a prescription drug, problems and inefficiencies within the agency may still serve to hamper effective regulatory decisions.¹¹ For example, the FDA's safety decisions regarding the painkilling drug Vioxx allegedly involved interpretation inconsistencies between agency officials. Research by an FDA staff member suggested serious cardiovascular risks were associated with the use of the Merck drug.¹² The researcher's supervisors allegedly

⁷ Fontanarosa et al., *supra* note 3, at 2647.

⁸ Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801(a)(2), 121 Stat. 823, 905.

⁹ *See id.* § 801(j)(2)(C). Under this law, the pharmaceutical company is obligated to report information about various aspects of the nature of any clinical trials the company undertakes. This data include basic information about the methodology of the study and the subsequent results. *Id.* § 801(j)(3)(D)(iii).

¹⁰ Fontanarosa et al., *supra* note 3, at 2647.

¹¹ This lack of effective regulatory decisions is not limited to prescription drugs. The FDA has recently advised consumers to discontinue using fourteen Hydroxycut products, which are widely used, over-the-counter dietary supplements for weight loss. Sandra Young, *Stop Using Hydroxycut Products, FDA Says*, CNN.COM, May 1, 2009, available at <http://www.cnn.com/2009/HEALTH/05/01/hydroxycut.fda.recall/index.html>. While the FDA was commended by commentators and analysts for issuing such a warning based on reports the agency received revealing links between use of the supplements and liver damage, serious incidents of liver damage had already occurred as early as 2002. *Id.* (“The reports include the 2007 death of a 19-year-old man living in the Southwest, which was reported to the FDA in March [2002].”). This delay in the reporting of incidents and corresponding determinations must be significantly shortened.

¹² Anna Wilde Mathews, *FDA Officials Tried to Tone Down Report on Vioxx*, WALL ST. J., Oct. 8, 2004, at B2.

felt these risks were not as serious as their subordinate contended.¹³ Yet soon after this interoffice inconsistency, Merck voluntarily pulled the drug off the market due to significant cardiovascular risks associated with its use, which were similar to those proposed by the staff member.¹⁴ This Vioxx incident led Senate Finance Committee Chairman Charles E. Grassley to investigate why “[i]nstead of acting as a public watchdog, the Food and Drug Administration was busy challenging its own expert.”¹⁵ The FDA has a history of similarly questionable interpretations of probative evidence regarding a product’s safety for use in the market.¹⁶

Further, the pharmaceutical industry may exert significant influence over the determinations of the FDA, especially during the drug approval process. The FDA hires panels of experts to advise the agency about whether a drug should be approved for introduction into the market for consumers and about other questions generated by the FDA related to this primary inquiry.¹⁷ Federal law enumerates various conditions that must be satisfied when selecting the experts that will serve on such an advisory panel.¹⁸ The law mandates “[n]o member of a panel may vote on any matter where the member . . . could gain financially from the advice given to the Secretary.”¹⁹ The agency does have the ability to waive this requirement so long as the public is notified of the conflict of interest.²⁰ However, in the period between January 1, 1998, and June 30, 1999, alone, 92% of all FDA

¹³ *Id.*

¹⁴ Alice Dembner, *Maker Takes Vioxx off Market*, BOSTON GLOBE, Oct. 1, 2004, available at http://www.boston.com/news/nation/articles/2004/10/01/maker_takes_vioxx_off_market/. A Merck-sponsored study found Vioxx doubled the risk of stroke and heart attack in certain situations as compared to placebo. *Id.*

¹⁵ Mathews, *supra* note 12, at B2.

¹⁶ See, e.g., Liz Szabo, *FDA Ignored Evidence when Calling BPA Safe*, USA TODAY, Oct. 29, 2008, available at http://www.usatoday.com/tech/science/2008-10-28-bpa-fda_N.htm. The FDA advised consumers that bisphenol A, or “BPA,” was safe for use in various products used by consumers, including baby bottles. *Id.* Analysis by researchers skeptical of this advice concluded that BPA was potentially harmful to children at one-tenth of the amount considered safe when used in the manufacture of baby bottles. *Id.*

¹⁷ 21 U.S.C. § 355(n)(1) (2006).

¹⁸ 21 U.S.C. § 355(n)(3). These conditions mostly speak to the qualifications of the members of an advisory panel, including both fields of expertise and experience with specialties in the disease the proposed drug will be indicated to treat.

¹⁹ 21 U.S.C. § 355(n)(4).

²⁰ *Id.*

expert panel meetings had at least one expert with a financial conflict of interest.²¹

Relatedly, pharmaceutical companies have shown the capacity to not only influence FDA evaluations by indirectly influencing the experts on the panel, but they may also voice an opinion regarding who should be excluded from the panel. The exclusion of a noted cardiologist from an expert panel evaluating a blood-thinning drug in 2009 is a telling example demonstrating this influence.²² Dr. Sanjay Kaul had a history of criticizing Eli Lilly's clinical trials for the blood thinner under consideration.²³ Presumably for this reason, Eli Lilly informed the FDA that Dr. Kaul had an "intellectual bias" and should be excluded from the advisory panel.²⁴ The FDA followed Eli Lilly's advice, and the remaining experts on the panel, not surprisingly, unanimously approved the drug.²⁵ Dr. Janet Woodcock, the director of the drug division within the FDA, stated, "[a]t every step of the way errors were made by multiple parties not following the correct way of doing things, and that led to Dr. Kaul being disinvited from the advisory committee meeting."²⁶ Eli Lilly effectively influenced the regulatory efforts of the FDA by preventing the presence of a voice that was likely to be negative toward its proposed prescription drug.

In light of the current regulatory climate, this Comment argues for a new approach to the regulation of prescription drugs approved by the FDA for general sale. The author proposes a reorganization of the agency resulting in the creation of a division of the FDA that focuses solely on actively making regulatory decisions regarding postapproval pharmaceutical products. This new division should be granted the power to effectively gather information and enforce regulations against pharmaceutical companies without needing to consult with

²¹ Dennis Cauchon, *FDA Advisers Tied to Industry*, USA TODAY, Sept. 25, 2000, at 1A, available at <http://www.internetwks.com/pauling/fdaconflict.html>. Surprisingly, these conflicts occasionally involved experts who would assist a pharmaceutical company in the development of a drug and then serve on the expert advisory panel assembled by the FDA to evaluate the drug for approval. *Id.* This dual service has the potential to materially undermine the FDA's analysis for obvious reasons, including inherent conflicts of interest.

²² Matthew Perrone, *FDA Admits Error in Barring Doctor from Panel*, ASSOCIATED PRESS, Feb. 24, 2009, available at <http://www.sfgate.com/cgi-bin/article.cgi?f=/n/a/2009/02/24/financial/f103042S33.DTL&feed=rss.business>.

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ *Id.* (internal quotation marks omitted).

another agency or FDA division. The use of this power by a new division would significantly ameliorate much of the public distrust discussed previously.

Part I of this Comment focuses on the authority and obligations of the FDA under the Federal Food, Drug, and Cosmetic Act (FDCA) as that law pertains to the regulation of prescription drugs in two regards: the period of time prior to the FDA's approval allowing the drug to enter the market, or preapproval, and the period of time after this approval occurs, postapproval. This Part highlights the shortcomings of the current postapproval regulatory environment, which originate in the FDCA but also stem from the methods used to implement this law.

Part II examines the regulatory scheme that has developed in the absence of strong regulation by the U.S. government. Without strong federal regulation, state attorneys general have turned to unique and innovative legal enforcement efforts to ensure the trust of patients and physicians in their respective states in the safety of the prescription drugs sold there.

Based on the void in the current federal regulatory landscape, the author proposes a systematic solution for remedying the current, crucial FDA deficiencies in Part III. The FDA must be granted the power and tools to more effectively and accurately analyze and react to drug safety data. The FDA must become more specialized, and thus efficient, by dividing the monitoring of prescription drugs along logical lines—between preapproval and postapproval regulation. This division of labor exists to some extent in the current scheme, but the power to make decisions based on emerging safety data must be fully vested in the proper subdivision of the agency. By enacting this solution, the federal government will create a system of postapproval drug regulation that will restore the American public's trust in the safety of the products that impact the most important possession of a constituent: mortality.

I

REGULATORY OBLIGATIONS OF PHARMACEUTICAL COMPANIES

A. New Drug Applications

Under the FDCA, a pharmaceutical company must receive permission from the FDA before it can market a drug in the United

States.²⁷ Specifically, the FDCA prescribes that “[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.”²⁸ The pharmaceutical company sponsoring the drug must provide the FDA with information, typically gathered through extensive clinical testing, regarding the drug’s efficacy and safety for its proposed uses.²⁹ The FDA must then receive a new drug application (NDA) from the sponsor outlining whether the clinical tests show the “drug is safe for use and whether such drug is effective in use.”³⁰ The composite documents included in an NDA should provide a full report of any clinical tests undertaken, a report on the results of any animal testing, and an overview explaining how the prescription drug behaves in the body.³¹

During the NDA process, the FDA also requires the sponsor company to provide a proposal for the prescription drug’s labeling, which should allow the agency to fully assess the effectiveness of the label.³² The FDA will then sanction the proposed labeling for the drug if the labeling adequately indicates the approved uses, the approved population, the appropriate warnings, and other important information about the drug that the agency concludes should be available to the general public.³³

The clinical studies used in the NDA application are controlled by the sponsor and tend to engage a few thousand subjects over a short period of time.³⁴ Based on their scope, these clinical studies are fundamentally incapable of adequately reflecting the likely safety issues that inevitably arise when the appropriate population in the

²⁷ See 21 U.S.C. § 355(a) (2006).

²⁸ *Id.*

²⁹ 21 C.F.R. § 312.23 (2009).

³⁰ 21 U.S.C. § 355(b)(1)(A).

³¹ See U.S. Food & Drug Admin., New Drug Application (NDA), available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm> (last visited Mar. 9, 2010).

³² David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 470 (2008).

³³ Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 FOOD & DRUG L.J. 1, 4 (2007).

³⁴ Charles Steenburg, *The Food and Drug Administration’s Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 297 (2006).

general public uses the drug, which could be a staggering number of patients. In 1964, then-FDA Commissioner George P. Larrick informed a subcommittee of the House Committee on Government Operations that the best “clinical investigation will reveal only a fraction of the information that emerges during the course of a drug’s general marketing and use.”³⁵ This sentiment is echoed by another expert on the matter, William Schultz, who stated that these preapproval investigations

can detect drug-related injuries that occur at a rate of between one in 500 and one in 1,000. Yet, if the drug is used by 200,000 people . . . a serious adverse event appearing in as few as one in 10,000 people is very significant, since it would occur 20 times. These rare reactions can be identified only after a drug has been widely used.³⁶

Further, preapproval clinical tests are unable to detect serious adverse events that occur in a subpopulation not represented in the study (the elderly, for example) and that occur only after use for a long period of time or, more likely, that occur somewhat infrequently.³⁷ Nonetheless, the FDA’s safety and efficacy evaluation of a new drug is based largely, if not entirely, on the information garnered by those clinical trials. Therefore, the FDA’s approval should not be considered a guarantee that the drug is safe for use.³⁸ For example, one study involving “biologicals,” drugs with an active substance produced by a biological source, in the United States and the European Union found that 23.6% of the drugs studied were subject to safety-related postapproval regulations, including

³⁵ *Id.*

³⁶ William B. Schultz, *How to Improve Drug Safety*, WASH. POST, Dec. 2, 2004, at A35, available at <http://www.washingtonpost.com/wp-dyn/articles/A26865-2004Dec1.html>.

³⁷ Kessler & Vladeck, *supra* note 32, at 471.

³⁸ See Gregory D. Curfman et al., *Why Doctors Should Worry About Preemption*, 359 NEW ENG. J. MED. 1, 2 (2008) (showing the safety issues that evolved for four prescription drugs that were on the market between a year and a half and fifteen years; two of these drugs were removed from the market altogether). Interestingly, in the case of medical devices, the U.S. Supreme Court recently decided that FDA approval precluded suit by patients against manufacturers. *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008). This ruling places a new strain on the FDA’s resources because the FDA’s approval of a device must effectively ensure the device’s safety without the continuous scrutiny of private litigation. Stuart O. Schweitzer, *Trying Times at the FDA—The Challenge of Ensuring the Safety of Imported Pharmaceuticals*, 358 NEW ENG. J. MED. 1773, 1773, 1776 (2008).

withdrawals from the market.³⁹ The limited scope of preapproval clinical trials creates an accentuated need for postapproval surveillance of prescription drugs that adequately safeguards the general public from unknown safety risks.

The preapproval process is unlikely to be significantly altered due to concerns that a more thorough process would result in serious health risks to the subjects of the trials. Prior to approval, pharmaceutical companies must conduct various “Phase” trials—clinical trials with increasing breadth and length to prove the overall risk-benefit of the drug. The purpose of Phase I trials is to determine basically how the drug will interact with human subjects.⁴⁰ Phase II trials involve a larger number of subjects that are suffering from the disease or condition for which the drug will be potentially approved to remedy.⁴¹ The final preapproval clinical trial is a Phase III study, which involves a larger number of subjects and is utilized to obtain more definite evidence of the overall risk-benefit profile of the drug.⁴²

Historically, critics of the current drug approval process argued that Phase IV trials—larger, postapproval clinical trials carried out by the sponsor—could serve an important function as an alternative to the traditional NDA process for the approval of life-saving drugs.⁴³ These critics were interested in both the speedy approval of drugs and the avoidance of any ethical dilemma arising from the untimely withholding of this important type of drug. In 2005, the FDA required approximately 57% of NDA sponsors to conduct some type of Phase IV trial after approval.⁴⁴ As discussed later, these obligations are rarely fulfilled as the FDA’s current organization undermines effective enforcement and monitoring of the trials. When used in conjunction with the passive gathering of safety information from health professionals and consumers, the use of Phase IV trials is one of the most effective means of analyzing larger safety risks in the general population of drug users.

³⁹ Thijs Giezen et al., *Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union*, 300 JAMA 1887, 1887 (2008). The biologicals in this study were approved between January 1995 and June 2007. *Id.*

⁴⁰ ClinicalTrials.gov, U.S. Nat’l Insts. of Health, Glossary of Clinical Trials Terms, <http://clinicaltrials.gov/ct2/info/glossary> (last visited Mar. 9, 2010).

⁴¹ *Id.*

⁴² *Id.*

⁴³ See Steenburg, *supra* note 34, at 319–20.

⁴⁴ *Id.* at 325. This conclusion results from an informal analysis of the NDAs filed in 2005. *Id.* at 325 n.319.

B. Postapproval Surveillance

Pharmaceutical companies are under a variety of obligations after a prescription drug receives approval by the FDA to enter the market. As discussed above, a full understanding of a drug's safety profile is almost impossible to establish based on the limited number of selected participants in the clinical trials used to support the FDA's decision to approve a new drug.⁴⁵ A complete understanding only becomes apparent as the general populace, without any selection process, uses the drug.⁴⁶

Understandably, federal law requires manufacturers of approved drugs to maintain all records of data and information relating to the drug's safety once it is introduced into the market.⁴⁷ This information should be sufficiently complete to allow the FDA, after reviewing it, to immediately suspend the drug's sale if the data show that the drug is an "imminent hazard to public health."⁴⁸ Essentially, the pharmaceutical company has an obligation under federal law to relay any information about adverse events reported to the company by physicians and others involved with the prescription drug to the FDA.⁴⁹ In the case of reports of serious and unexpected adverse events arising from the use of the particular drug, the company must forward the information to the FDA within fifteen days of initial receipt.⁵⁰ After forwarding, the pharmaceutical manufacturer must

⁴⁵ See Catherine D. DeAngelis & Phil B. Fontanarosa, *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 JAMA 1939, 1939 (2008).

⁴⁶ *Id.* This may not necessarily be the case for certain drugs with specialized indications. For example, certain prescription birth control drugs will only be used by a specialized segment of the population: younger women. In these situations, clinical trials prior to approval may be significantly more accurate in predicting the safety of the drug as the affected population is more particular and thus easier to generalize.

⁴⁷ 21 U.S.C. § 355(k)(1) (2006).

⁴⁸ 21 U.S.C. § 355(e), (k)(1).

⁴⁹ 21 C.F.R. § 314.80(c) (2009). An adverse event is not defined expressly in the federal regulations.

⁵⁰ 21 C.F.R. § 314.80(c)(1)(i). The commonly used definition is:

any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product

U.S. DEP'T OF HEALTH & HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY E6 GOOD CLINICAL PRACTICE: CONSOLIDATED GUIDANCE 2 (1996), available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/UCM129515.pdf>.

then conduct further investigations into the nature and circumstances of the adverse event—the results of which must be subsequently forwarded to the FDA within fifteen days.⁵¹ Less serious adverse reactions must be reported to the FDA either quarterly or annually depending on the length of time the prescription drug has been on the market.⁵² The pharmaceutical company is also required to provide the FDA with an annual report summarizing new information about the drug's efficacy, safety, and labeling from the previous year, including an explanation of the actions the company will be taking as a result.⁵³

These obligations seem stringent, but two distinct inadequacies prevent this passive reporting from being truly effective in practice, namely an inefficient and underfunded process and a general lack of reporting of adverse events by companies. Tellingly, a study by the U.S. Government Accountability Office (GAO) found that the “FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues.”⁵⁴ Although the FDA is responsible for ensuring the safety of a collection of products that accounts for approximately twenty percent of total consumer spending,⁵⁵ the FDA's budget in 2005 was less than 1/50 the budget of the U.S. Department of Agriculture.⁵⁶ Also, pharmaceutical companies have no independent obligation to establish a system that will track adverse events or otherwise improve their efforts to gather adverse event data.⁵⁷

In 2002, U.S. Representative Henry Waxman stated “the FDA estimates that it hears of less than 1 percent of serious adverse reactions.”⁵⁸ This lack of reporting likely stems from the practical problems facing physicians and others who attempt to report, including the inherent difficulty in determining if the adverse event

⁵¹ 21 C.F.R. § 314.80(c)(1)(ii).

⁵² 21 C.F.R. § 314.80(c)(2).

⁵³ 21 C.F.R. § 314.81(b)(2)(i).

⁵⁴ U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 5 (2006), available at <http://gao.gov/new.items/d06402.pdf>.

⁵⁵ Eve E. Slater, *Today's FDA*, 352 NEW ENG. J. MED. 293, 293 (2005).

⁵⁶ *Id.* at 294. The FDA also employed a tenth the workforce of the U.S. Department of Agriculture. *Id.*

⁵⁷ Steenburg, *supra* note 34, at 298.

⁵⁸ *Reauthorization of the Prescription Drug User Fee Act: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 107th Cong. 49 (2002) (statement of Rep. Henry Waxman).

occurred because of the use of the prescription drug or if the event is merely a symptom of the infliction or illness that the patient is suffering. Also, the adverse event may be so common in the general populace that physicians may not feel compelled to report it to the drug's manufacturer.⁵⁹ For example, Merck withdrew Vioxx from the market after a clinical trial revealed a significantly increased risk of heart attacks resulting from the use of the drug when compared to a placebo.⁶⁰ Because heart attacks are such a common occurrence in the general public, physicians did not see the link before the study between the increase in the occurrence of heart attacks in Vioxx users and their use of the pain medication.⁶¹ For those reasons, the inefficient process and the spontaneous and voluntary reporting used in postapproval regulation have proved insufficient to adequately protect the public.

Another important focus of the FDA in postmarket drug regulation is the regulation of modifications to a drug's labeling. Federal law requires pharmaceutical companies to seek approval of most proposed label changes for a prescription drug, including major labeling changes relating to a drug's safety.⁶² But there are a variety of changes that may be made without the FDA's prior authorization to allow the company to quickly provide the most current safety information to physicians who prescribe and patients who use the drug.⁶³ No prior authorization is needed for changes

[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction [for which there is the evidence of a causal association]; . . . [t]o add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose; . . . [t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product; . . . [and t]o delete false, misleading, or unsupported indications for use or claims for effectiveness⁶⁴

In fact, federal law requires pharmaceutical companies to report changes to the labeling of a prescription drug that reflect significant hazards once a reasonable causal connection between the hazard and

⁵⁹ Steenburg, *supra* note 34, at 299.

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² 21 C.F.R. § 314.70(b)(2)(v) (2009).

⁶³ Kessler & Vladeck, *supra* note 32, at 472–73.

⁶⁴ 21 C.F.R. § 314.70(c)(6)(iii)(A)–(D).

the drug has been established.⁶⁵ But, as discussed more fully below, this regulation has also proved ineffective, and, thus, the impetus for label changes normally comes from other enforcement actors.

II

SETTLEMENT AGREEMENTS OF THE STATE ATTORNEYS GENERAL (OUTSIDE OF THE FDA'S PURVIEW)

The void created by ineffective federal surveillance of prescription drugs after approval has been filled by the novel enforcement actions of various state attorneys general.⁶⁶ Over the last decade, the litigation efforts of state attorneys general against product manufacturers have dramatically altered the regulatory landscape in many industries.⁶⁷ This dramatic change is the result of a peculiar characteristic of lawsuits brought by the state attorneys general, which is particularly prevalent when multiple states join together in such suits.⁶⁸ This characteristic is the elevated risk to the future vitality of the business should the litigation proceed to a negative result. Few defendant manufacturers could possibly risk allowing the lawsuits brought by the state attorneys general to go to trial.⁶⁹ Unlike actions brought by private, individual plaintiffs, the possible damages resulting from a loss in these trials could be crippling for the manufacturer because the alleged harm will have been suffered by millions of each state's residents.⁷⁰ Further, class action lawsuits brought by private plaintiffs would inevitably follow a successful state litigation, utilizing the former action's groundwork.

Rather than chance huge damages payouts and considerable adverse publicity, manufacturers acquiesce to the often-overwhelming compulsion to settle with the state attorneys general. More importantly for our purposes, these actions, and their subsequent settlement agreements, often go beyond merely addressing damages and enforcing current regulations by effectively imposing new

⁶⁵ See 21 C.F.R. § 314.80(c)(2)(i).

⁶⁶ MCDERMOTT WILL & EMERY, *MERCK SETTLES VIOXX LITIGATION WITH STATE ATTORNEYS GENERAL: AN ANALYSIS 2* (2008), available at <http://www.mwe.com/info/news/wp0508a.pdf>.

⁶⁷ Donald G. Gifford, *Impersonating the Legislature: State Attorneys General and Parens Patriae Product Litigation*, 49 B.C. L. REV. 913, 914 (2008).

⁶⁸ See *id.* at 915.

⁶⁹ *Id.* at 916.

⁷⁰ *Id.*; see also *In re Rhone-Poulenc Rorer, Inc.*, 51 F.3d 1293, 1298 (7th Cir. 1995) (discussing similar class action lawsuits as eventually coercing "blackmail settlements").

“regulatory-like” controls and requirements on companies regarding future practices and products.⁷¹ For example, as discussed further below, the settlement agreement between Merck and the state attorneys general in the Vioxx litigation required the company to make additional reports to the FDA regarding advertising campaigns that were not required by the federal regulations then in effect.⁷² Prior to discussing the current situation involving pharmaceutical regulation, a brief analysis of the evolution of the efforts of state attorneys general in other industries must be considered to provide context.

A. The Foundation of State Attorney General Regulation: Tobacco Lawsuits

On May 23, 1994, Mississippi Attorney General Mike Moore filed a complaint against several major tobacco companies alleging that the companies harmed the state by causing its citizens to incur tobacco-caused illnesses.⁷³ His argument for recovery was based on the allegation that the state incurred substantial costs providing an increased amount of health care to tobacco users while the tobacco companies profited from their harmful conduct.⁷⁴ Additionally, the companies actively prevented the discovery of this harm, specifically the relationship between tobacco use and certain ailments, by violating a promise to provide independent scientific data about the effects of smoking to the citizens of Mississippi.⁷⁵ The data the companies did provide effectively covered up the results of studies proving the detrimental effects of smoking.⁷⁶ Moore argued that the companies’ conduct, especially the fabricated study results, violated Mississippi’s laws against unfair and deceptive practices as well as

⁷¹ Deborah R. Hensler, *The New Social Policy Torts: Litigation as a Legislative Strategy Some Preliminary Thoughts on a New Research Project*, 51 DEPAUL L. REV. 493, 498 (2001).

⁷² See Stipulated General Judgment at 1, 6, Oregon *ex rel.* Hardy Myers v. Merck & Co., No. 08C16426 (Or. Cir. Ct. 2008) [hereinafter Merck Stipulated General Judgment], available at http://www.merck.com/newsroom/vioxx/pdf/ag_document.pdf.

⁷³ See generally Complaint, Moore *ex rel.* Mississippi v. Am. Tobacco Co., No. 94-1429 (Miss. Ch. Ct. 1994), available at http://www.library.ucsf.edu/sites/all/files/ucsf_assets/ms_complaint.pdf.

⁷⁴ See *id.* ¶ 2.

⁷⁵ See *id.* ¶¶ 43–47.

⁷⁶ *Id.* ¶ 65.

public nuisance laws.⁷⁷ He summarized the public nuisance allegation as follows:

[T]he defendants have intentionally and unreasonably interfered with the public's right to be free from unwarranted injury, disease and sickness, and have caused damage to the public health, the public safety and the general welfare of the citizens of Mississippi, and have thereby wrongfully caused the State to expend millions of dollars in support of the public health and welfare.⁷⁸

Millions in expenses accrued mostly in the form of disbursements through Medicaid for the treatment of smoking-related, if not caused, diseases.⁷⁹ Strategically, Moore intentionally brought claims for state law violations to avoid the pitfalls that had prevented numerous private litigants from recovering against the tobacco industry—the primary pitfalls being unsuccessful efforts of either proving causation of any illnesses or overcoming the affirmative legal defense of assumption of the risk employed by the manufacturers.⁸⁰

The major tobacco products manufacturers in the United States signed an agreement with Mississippi and the forty-five other state attorneys general, who joined the lawsuit against the companies to recover for the public harm that resulted from the companies' fraudulent concealment of the dangers involved with smoking.⁸¹ This settlement agreement forced the tobacco companies to pay an extremely large sum of money to the aggrieved parties.⁸² Specifically, in exchange for a bar on the states pursuing subsequent Medicaid claims in the future against the companies, the defendants have had to pay \$206 billion over a twenty-five-year span.⁸³

More importantly, the settlement also required the major tobacco companies to substantively reform their practices.⁸⁴ These reforms

⁷⁷ *Id.* ¶¶ 76, 90.

⁷⁸ *Id.* ¶ 90.

⁷⁹ Victor E. Schwartz et al., *Tort Reform Past, Present and Future: Solving Old Problems and Dealing with "New Style" Litigation*, 27 WM. MITCHELL L. REV. 237, 255–56 (2000).

⁸⁰ Gifford, *supra* note 67, at 922.

⁸¹ Michael I. Krauss, *Regulation Masquerading as Judgment: Chaos Masquerading as Tort Law*, 71 MISS. L.J. 631, 656–57 (2001) (arguing the lack of foundation for the government's case).

⁸² Hensler, *supra* note 71, at 493.

⁸³ Robert A. Levy, *The New Business of Government Sponsored Litigation*, 9 KAN. J.L. & PUB. POL'Y 592, 593 (2000).

⁸⁴ See NAT'L ASS'N OF ATTORNEYS GEN., MASTER SETTLEMENT AGREEMENT 14–28, available at <http://www.naag.org/backpages/naag/tobacco/msa/msa-pdf/MSA> with Sig

include the following: a prohibition on targeting children in the advertising of tobacco products, including a prohibition on the use of cartoons in advertising;⁸⁵ limitations on the ability of the tobacco companies to sponsor certain events using the companies' brand names, including most athletic events;⁸⁶ a ban on merchandise with the companies' brand names;⁸⁷ and a requirement that the companies not sell cigarettes in a pack containing less than twenty.⁸⁸ Antismoking advocates had tried for years to obtain similar restraints on the tobacco industry from Congress, to no avail, presumably due to lobbying efforts.⁸⁹

The actions of the state attorneys general against the tobacco industry have served as the model and impetus for subsequent regulatory lawsuits against other industries.⁹⁰ Shortly after the tobacco settlement, fifty state attorneys general participated in a strategy session to discuss future industries to target and reform.⁹¹ "Reports suggest that these targets could include HMOs, automobiles, chemicals, alcoholic beverages, *pharmaceuticals*, Internet providers, 'Hollywood,' video game makers, and even the dairy and fast food industries."⁹²

B. State Attorneys General Tackle Prescription Drugs

The various state attorneys general have displayed an interest in testing the outer bounds of their "regulatory" ability in various domestic industries through the use of a litany of substantive laws, particularly in the pharmaceutical field.⁹³ For example, in 2001, the

Pages and Exhibits.pdf/download (describing the restrictions on defendants' behavior agreed to as part of the settlement).

⁸⁵ *Id.* at 14.

⁸⁶ *Id.*

⁸⁷ *Id.* at 18–19.

⁸⁸ *Id.* at 21 (providing that this packaging requirement would only be effective until December 31, 2001).

⁸⁹ Hensler, *supra* note 71, at 493.

⁹⁰ See Sherman Joyce & Michael Hotra, *Mississippi's Civil Justice System: Problems, Opportunities and Some Suggested Repairs*, 71 MISS. L.J. 395, 411–13 (2001).

⁹¹ *Id.* at 412.

⁹² Schwartz et al., *supra* note 79, at 258 (emphasis added).

⁹³ See, e.g., Office of the Comptroller of the Currency v. Spitzer, 396 F. Supp. 2d 383, 407 (S.D.N.Y. 2005) (preempting the New York Attorney General from enforcing state fair-lending laws against national banks). In 2006, the California Attorney General sued automobile makers using various tort laws with the goal of regulating automobile emissions. Gifford, *supra* note 67, at 914–15.

West Virginia Attorney General filed suit against the pharmaceutical company that manufactured the prescription drug OxyContin alleging both violations of the West Virginia Consumer Credit Protection Act and various common law torts.⁹⁴ The attorney general alleged that the manufacturer of the drug made various misrepresentations concerning the drug's uses and safety, especially in reference to the occurrence of addiction at various dosages of the drug.⁹⁵ The deception allegedly led to an increasing number of people becoming addicted to OxyContin, which in turn led to a significant injury to the state in the form of a marked increase in social problems, including crimes.⁹⁶ These social problems included "drug abuse and criminal acts to obtain OxyContin."⁹⁷ The West Virginia Attorney General eventually settled the claim with the manufacturer for ten million dollars.⁹⁸

A decade before the OxyContin settlement, approximately twenty states created an informal consumer protection work group to pursue various consumer protection law enforcement actions involving healthcare issues.⁹⁹ As shown by the OxyContin suit, this group placed, and still pursues, a heavy emphasis on the oversight of prescription drugs after their approval in the absence of effective supervision by the FDA.

The state attorneys general use consumer protection laws to fill the federal supervisory void by enforcing provisions of the FDCA and other FDA regulations.¹⁰⁰ The enforcement and regulatory scheme employed by the state attorneys general is a direct descendant of the tobacco regulation lawsuits. While this undertaking is certainly controversial and vulnerable to challenge, it serves to hold pharmaceutical companies accountable for overlooked violations of

⁹⁴ See Complaint at 12–30, West Virginia *ex rel.* McGraw v. Purdue Pharma L.P., No. 01-C-137-S (W. Va. Cir. Ct. 2001), available at <http://www.cmht.com/pdfs/oxycontin-cmpl.pdf>.

⁹⁵ *Id.* at 2.

⁹⁶ *Id.*

⁹⁷ *Id.*

⁹⁸ *OxyContin Lawsuit Is Settled: Purdue Pharma to Pay State \$10 Million*, CHARLESTON GAZETTE, Nov. 6, 2004, at 1A.

⁹⁹ David Woodward, *Recent Multistate Enforcement Initiatives: Prescription Drug Promotional Practices*, 50 FOOD & DRUG L.J. 295, 295, 295 n.1 (1995).

¹⁰⁰ See, e.g., Stipulated General Judgment at 4–14, Oregon *ex rel.* Hardy Myers v. Pfizer, Inc., No. 08C23533 (Or. Cir. Ct. Oct. 22, 2008) [hereinafter Pfizer Stipulated General Judgment], available at http://www.doj.state.or.us/releases/pdf/pfizer_stip_judg_complaint.pdf.

federal law. This scheme, as discussed below, enables the state attorneys general to take an active role in the postapproval regulation of prescription drugs.

The key component of the scheme is regulatory-type settlements. When the state attorneys general believe or get the sense that the FDCA is not sufficiently protecting consumers in the pharmaceutical industry, they subtly supplement the law with substantive terms included in settlements that resolve consumer protection actions brought by multiple states acting jointly. The impetus for supplementing federal law stems from the tobacco regulation litigation, as demonstrated by the various prohibitions on advertising included in the settlement between the companies and the state attorneys general, especially those involving advertising aimed at youth.¹⁰¹ Some proponents of the new regulations created in the tobacco settlements believed “[t]he tobacco industry’s influence over federal and state legislators makes it enormously difficult, if not impossible, for effective tobacco control legislation to be passed at the federal or state level.”¹⁰² The state attorneys general managed to circumvent the influence of the pharmaceutical industry by imposing needed reform on the industry.

For example, the New York Attorney General filed suit against Glaxo in 2004, alleging the pharmaceutical company failed to reveal important clinical trial results evaluating off-label uses of its approved drug Paxil.¹⁰³ New York argued that Glaxo threatened public health by withholding information about off-label uses—an allegation that arguably cannot be squared with Glaxo’s obligations under FDA regulations, which prohibit pharmaceutical companies from discussing off-label aspects of an approved drug.¹⁰⁴ The rationale for the FDA’s policy restricting such communication stems from the agency’s goal of preventing patients from spending more money than necessary on medication for its off-label uses, therefore experiencing

¹⁰¹ In fact, the tobacco industry was subjected to heavy scrutiny by Congress, yet the legislative body decided not to pass such strict regulations on advertising. See Gifford, *supra* note 67, at 924.

¹⁰² Graham E. Kelder, Jr. & Richard A. Daynard, *The Role of Litigation in the Effective Control of the Sale and Use of Tobacco*, 8 STAN. L. & POL’Y REV. 63, 63 (1997).

¹⁰³ Hall & Sobotka, *supra* note 33, at 2. A prescription drug’s off-label purposes are uses made of the drug by the general public that have not been approved by the FDA. Complaint at 3, Oregon *ex rel.* Hardy Myers v. Pfizer, Inc., Case No. 08C23533 (Or. Cir. Ct. Oct. 22, 2008) [hereinafter Pfizer Complaint], available at http://www.doj.state.or.us/releases/pdf/pfizer_complaint.pdf.

¹⁰⁴ Hall & Sobotka, *supra* note 33, at 2.

harmful side effects from unevaluated uses of the drugs and even potentially dying from a misuse of the drug.¹⁰⁵ Glaxo eventually settled with the New York Attorney General and agreed to release all of the clinical trial information about Paxil, including information about the off-label uses.¹⁰⁶ The state attorney general was obviously convinced that the FDA regulations were insufficient to protect the citizens of New York and, in a subtle way, circumvented the agency's authority by creating new substantive obligations for Glaxo in the future.¹⁰⁷ The strategy of procuring settlement with pharmaceutical companies to fill the void left by a lack of FDA regulation had proved to be a viable way to ensure the company's actions were being sufficiently monitored.

C. Recent Enforcement Actions: The Vioxx Settlement

The strategy discussed above has been utilized in recent years to further a variety of enforcement and regulation interests of state attorneys general, normally under the leadership of the Oregon Attorney General. In May 2008, Merck & Co., Inc., (Merck) entered into a stipulated general judgment with a coalition of twenty-nine states and the District of Columbia concerning the prescription drug Vioxx.¹⁰⁸ The Oregon-led coalition alleged that Merck violated their respective state consumer protection statutes through a deceptive advertising campaign that misrepresented Vioxx's cardiovascular safety while the drug was on the market.¹⁰⁹ On September 30, 2004, after a Data and Safety Monitoring Board for a Merck-sponsored clinical trial of Vioxx found that subjects had an increased risk of serious cardiovascular ailments as compared to subjects taking a placebo, Merck voluntarily withdrew the pain drug from the market.¹¹⁰ As discussed above, the FDA found the safety evidence

¹⁰⁵ *Id.*

¹⁰⁶ *Id.* at 3.

¹⁰⁷ For an interesting analysis of the constitutionality of the FDA's limitations for off-label advertising and a discussion of the implications of these limits for First Amendment jurisprudence, see *id.* at 3, 10–48.

¹⁰⁸ See Merck Stipulated General Judgment, *supra* note 72, at 3.

¹⁰⁹ Press Release, Attorney Gen. of Mass., Attorney General Martha Coakley Files Judgment Against Merck Pharmaceutical for the Company's Deceptive Marketing of Vioxx (May 20, 2008), available at http://www.mass.gov/?pageID=cagopressrelease&L=1&L0=Home&sid=Cago&b=pressrelease&f=2008_05_20_vioxx_judgment&csid=Cago.

¹¹⁰ U.S. Food & Drug Admin., *Merck Withdraws Vioxx; FDA Issues Public Health Advisory*, FDA CONSUMER, Nov.–Dec. 2004, available at http://findarticles.com/p/articles/mi_m1370/is_6_38/ai_n7069493/.

from various clinical trials prior to Merck's voluntary withdrawal inconclusive.¹¹¹

Merck's settlement with the state attorneys general is significant for both the monetary and substantive terms it contained. The coalition of state attorneys general received a \$58 million monetary settlement that was to be divided among the thirty members.¹¹² At the time, the payment was the largest financial settlement for consumer protection violations based on deceptive advertising of a prescription drug.¹¹³ But the more material aspect of the settlement is the substantive terms used by the coalition to "[position] themselves as potent enforcers in their own right who have the will and the means . . . to impose significant going-forward constraints on the pharmaceutical and device industries."¹¹⁴ It is important to note at the outset that the settlement terms apply prospectively to all of Merck's drugs as opposed to only drugs in a certain class, e.g., pain relievers. The substantive terms can be broken down into two somewhat distinct categories: increased ability for state attorneys general to enforce FDA regulations and new regulations of Merck's activities by which the company voluntarily agreed to abide.

The Merck settlement increases the ability of the state attorneys general to enforce regulations promulgated by the FDA.¹¹⁵ The settlement requires Merck to refrain from any advertising concerning the safety or efficacy of any FDA-approved drug that violates the FDCA and other FDA regulations.¹¹⁶ In accordance with the FDA Amendments Act of 2007, Merck must also submit information regarding clinical trial results to a registry established by the FDA.¹¹⁷ But, the settlement expressly states that it is not requiring Merck to violate the FDCA and the FDA's other regulations nor is it requiring Merck to fail to act as mandated by the FDCA and the FDA.¹¹⁸ Basically, the terms merely require Merck to abide by federal laws.

¹¹¹ See *supra* notes 12–16 and accompanying text.

¹¹² MCDERMOTT WILL & EMERY, *supra* note 66, at 2.

¹¹³ Press Release, Penn. Office of the Attorney Gen., Attorney General Corbett Announces a Multi-State, \$58 Million Settlement with Merck over Deceptive Advertising Concerning the Safety of Vioxx (May 20, 2008), available at <http://www.attorneygeneral.gov/press.aspx?id=3660>.

¹¹⁴ MCDERMOTT WILL & EMERY, *supra* note 66, at 2.

¹¹⁵ *Id.* at 2–3.

¹¹⁶ Merck Stipulated General Judgment, *supra* note 72, at 5.

¹¹⁷ *Id.* at 4–5.

¹¹⁸ *Id.* at 5–6.

Also for future validity, an important notion that emerges from these provisions in the settlement is the fact that “even though the settlement agreement was effected under the various state consumer protection statutes, [the agreement] largely sidesteps the entire preemption controversy.”¹¹⁹ Through the aforementioned settlement terms, the state attorneys general seem to have effectively put themselves in the FDA’s enforcement realm.¹²⁰ Any terms in the settlement that Merck violates can be directly enforced through a contempt proceeding in court because the settlement is contractually enforceable by the state attorneys general.¹²¹

The settlement also imposes new regulatory obligations on Merck that do not stem from federal law or regulations. As of this writing, pharmaceutical companies are under no obligation to submit their direct-to-consumer (DTC) advertising to the FDA prior to running the advertisement in any media.¹²² The argument against requiring the companies to make such a submission revolves around a concern that the terms are unconstitutional under the First Amendment.¹²³ But, in the settlement, Merck voluntarily agreed to “submit all new DTC television advertising campaigns for *any* Merck Product to FDA for pre-review, wait until Merck receives a response from FDA prior to running the advertising campaign, and to modify such advertising consistent with any written comments received from FDA.”¹²⁴ Based on Merck’s volition, the settlement likely avoids the First Amendment issues that prevent the imposition of federal regulations for DTC advertising, while also creating a type of “pocket veto” for the FDA regarding any new television advertising campaigns for Merck products.¹²⁵

¹¹⁹ MCDERMOTT WILL & EMERY, *supra* note 66, at 3; *see also* *Wyeth v. Levine*, 129 S. Ct. 1187, 1200 (2009) (finding that the FDCA does not preempt a claim for lack of adequate warning under state law). The settlement seems to provide the state attorneys general with an important enforcement role regardless of any future court decisions or legislation preempting the regulation of prescription drugs through state tort law claims. The state attorneys general need only rely on state contract law.

¹²⁰ Merck Stipulated General Judgment, *supra* note 72, at 2.

¹²¹ *Id.* at 3. It is worth noting the practical difficulties of bringing a contempt proceeding based on a violation of the settlement by Merck. Whether a trial court judge in a particular state—likely Oregon—could effectively handle such a proceeding is difficult to ascertain based on the strong interest of the FDA in any precedent that emerges from a decision regarding whether a company has violated its regulations.

¹²² *See* 21 U.S.C. § 352(n)(3)(a) (2006).

¹²³ MCDERMOTT WILL & EMERY, *supra* note 66, at 4.

¹²⁴ Merck Stipulated General Judgment, *supra* note 72, at 6 (emphasis added).

¹²⁵ *See* MCDERMOTT WILL & EMERY, *supra* note 66, at 4.

The state attorneys general also included other regulatory provisions in the settlement. One such provision imposes more stringent disclosure requirements for Continuing Medical Education (CME) presenters who may have a financial conflict of interest arising from a promotional relationship with Merck, including a requirement of a written disclosure of the conflict in the materials provided at the CME session.¹²⁶ These requirements were likely intended to flush out any prejudices that attendees should be made aware. Further, the settlement outlines the requirements that must be met for an individual to be identified as an author in a manuscript for a Merck-sponsored clinical trial.¹²⁷ A proposed author must have “made substantial contribution to the conception and design, or acquisition of data, or analysis and interpretation of data.”¹²⁸ This requirement reflects the concern of the state attorneys general with the rampant exercise of “ghostwriting.”¹²⁹ Ghostwriting refers to the practice in the pharmaceutical industry of writing manuscripts within the company and paying prominent scientists to be listed as authors when the manuscripts are published in scientific journals.¹³⁰ Documents uncovered as a result of Vioxx lawsuits showed Merck was actively ghostwriting.¹³¹ The settlement also imposes new constraints on Merck concerning the use of scientists with certain financial conflicts of interest on a Data Safety and Monitoring Board for a Merck-sponsored clinical trial.¹³² Once again, these constraints are intended to increase the objectivity of those controlling the results and completion of clinical trials.

As discussed in the tobacco context above, Merck was likely under intense financial and public relations pressure during the investigation by the state attorneys general, which led to a settlement with such wide-ranging and potentially damaging requirements regarding future practices.

¹²⁶ Merck Stipulated General Judgment, *supra* note 72, at 8.

¹²⁷ *Id.* at 10.

¹²⁸ *Id.*

¹²⁹ MCDERMOTT WILL & EMERY, *supra* note 66, at 6.

¹³⁰ Jonathan Bor, *Research Ghostwriting Common, Insiders Say: Drug Companies Seek Recognized Authors*, BALT. SUN, Apr. 18, 2008, at 1A, available at http://articles.baltimoresun.com/2008-04-18/news/0804180351_1_deangelis-merck-ghost-writing.

¹³¹ *See id.* Bor also provides insights from insiders in the clinical trial arena that suggest ghostwriting is a widespread practice throughout the pharmaceutical industry. *Id.*

¹³² Merck Stipulated General Judgment, *supra* note 72, at 9.

D. More Comprehensive Regulation: The Bextra Settlement

Shortly after the Merck settlement, pharmaceutical giant Pfizer faced similar financial and public relations pressure as the result of an investigation of its prescription drug Bextra. The FDA approved Bextra on November 16, 2001, for the relief of symptoms of various types of arthritis and menstrual pain.¹³³ Pfizer did not receive approval from the FDA for other indications it had proposed and actively sought, namely the treatment of general acute pain.¹³⁴ The FDA explicitly found the data submitted concerning the efficacy and safety of Bextra for the treatment of acute pain to be insufficient to warrant approval of the drug for that purpose.¹³⁵

A coalition of state attorneys general brought an action against Pfizer for violating state consumer protection laws based on the deceptive promotion of Bextra for “off-label” purposes.¹³⁶ In direct conflict with the FDA’s decision not to approve Bextra for the treatment of general acute pain, Pfizer allegedly promoted the drug for this off-label use through various means, including the following: distributing samples of Bextra to specialty physicians who do not normally treat patients suffering from arthritis or menstrual pain, which was the approved population for the drug; providing various gifts, mostly meals, to doctors who prescribed the drug to patients for off-label purposes; delivering print advertisements to physicians and consumers that highlighted Bextra’s efficacy for off-label uses; and promulgating a substantial number of copies of studies showing positive results for the drug’s treatment of acute pain without juxtaposing those studies with the numerous negative studies evaluating Bextra’s off-label uses.¹³⁷ This off-label advertising not only violated state consumer protection laws, it also violated federal regulations promulgated by the FDA.¹³⁸ In April 2005, the FDA asked Pfizer to voluntarily withdraw Bextra from the market based on safety concerns that were similar to those revealed in the use of

¹³³ Letter from Jonca Bull, Acting Dir., Office of Drug Evaluation, U.S. Food & Drug Admin., to Peter L. East, Assoc. Dir. of Regulatory Affairs, G.D. Searle & Co., at 1 (Nov. 16, 2001), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-341_Bextra_Approv.pdf.

¹³⁴ *Id.*; *see also* Pfizer Complaint, *supra* note 103, at 2–3.

¹³⁵ Letter from Jonca Bull, *supra* note 133, at 3.

¹³⁶ Pfizer Complaint, *supra* note 103, at 18–21.

¹³⁷ *Id.* at 3–4.

¹³⁸ 21 C.F.R. § 202.1(e)(4) (2009).

Vioxx—a drug in the same class as Bextra.¹³⁹ The FDA, however, never investigated the off-label advertising violations of Bextra, even though they were allegedly widespread.

Undaunted, state attorneys general took the initiative to investigate these violations and brought suit under their respective consumer protection laws. Eventually a coalition of thirty-two states and the District of Columbia entered into a settlement with Pfizer that imposed terms similar to the Merck settlement.¹⁴⁰ The states added an interesting twist to the new settlement's terms that seemed to address a perceived difficulty with enforcing the Merck settlement. Although the Merck settlement contains important obligations on the part of the company, the state attorneys general have few resources to devote to the monitoring of Merck's compliance, especially in the current economic climate. Most states certainly have the ability to subpoena information from the company at any time to obtain information and communications relating to potential violations.¹⁴¹ Yet the states would likely need some sort of "tip" or other indication that such unlawful conduct was occurring to know what documents to subpoena and when to make the request.

To account for this difficulty in enforcing the terms of the Pfizer settlement, which arguably created new regulations to which Pfizer must adhere, the state attorneys general inserted self-reporting mechanisms in the agreement. For example, the Pfizer settlement contains a provision requiring the company to submit any DTC television campaign to the FDA for review and to modify the campaign in accordance with the FDA's recommendations prior to running it.¹⁴² Unlike the Merck settlement, Pfizer may run an

¹³⁹ U.S. FOOD & DRUG ADMIN., ALERT FOR HEALTHCARE PROFESSIONALS: VALDECOXIB (MARKETED AS BEXTRA) (Apr. 7, 2005), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124649.htm> (concluding "the overall risk versus benefit profile of Bextra is unfavorable"); see also *supra* note 110 and accompanying text. In all fairness to Pfizer, the company decided to heed the FDA's advice and removed the product from the market despite voicing disagreement with the FDA's decision.

¹⁴⁰ Pfizer Stipulated General Judgment, *supra* note 100, at 3–14. The states were: Alaska, Arizona, Arkansas, California, Connecticut, Florida, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Montana, Nebraska, New Jersey, New York, New Mexico, Nevada, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Washington, and Wisconsin. *Id.*

¹⁴¹ See, e.g., OR. REV. STAT. § 646.618(1) (2009).

¹⁴² Pfizer Stipulated General Judgment, *supra* note 100, at 6. Similar terms were used in the Merck settlement. See *supra* note 72 and accompanying text.

advertisement after waiting a reasonable time—forty-five days—without receiving the FDA’s response, but the company must provide written notice to a smaller executive group of signatory states to alert the state coalition that the FDA did not provide any of the requested guidance.¹⁴³ Pfizer would also have to include any material submitted to the FDA concerning the request for a review of the proposed advertising with the notice.¹⁴⁴

While states may face similar resource limitations in monitoring Pfizer’s compliance with this notice requirement, the settlement establishes an affirmative duty on the part of the company to, in essence, alert the state attorneys general of a potential violation of the settlement terms. At a minimum, the state attorneys general could begin focusing heightened attention and effort on investigating the compliance of Pfizer’s advertising efforts after receiving this alert. The notice requirement demonstrates another step by the states to fill the perceived gap in the FDA’s enforcement efforts. Basically, the two governmental bodies are receiving similar information, but the states are more capable and motivated to enforce regulations, especially with the potential financial and publicity benefits that inherently result from efforts to keep the citizens of the states safe.

E. Obstacles for Regulatory Settlements

The settlements between Merck and Pfizer and the state attorneys general were motivated by a general lack of belief that the FDA can, or will, effectively ensure a satisfactory level of safety in the pharmaceutical industry. In fact, some commentators have asserted that the fact that “State AGs, individually and collectively, can now march into court under [the] FDA’s own regulations effectively means that there is a ‘new cop on the beat’ ready, willing and able to pursue actions for alleged advertising violations whenever they believe [the] FDA is not doing the job properly.”¹⁴⁵

As discussed above, the avenue of choice for state attorneys general to regulate the pharmaceutical companies is claims under their respective consumer protection statutes. There is a strong argument that these consumer protection laws were originally enacted by states to fill a gap in product safety areas where industry is not

¹⁴³ Pfizer Stipulated General Judgment, *supra* note 100, at 6.

¹⁴⁴ *Id.*

¹⁴⁵ MCDERMOTT WILL & EMERY, *supra* note 66, at 5.

closely regulated and supervised by the federal government.¹⁴⁶ Based on the legislative intent behind enacting these statutes, there is an inherent tension involved with claims by the state attorneys general alleging misleading representations or promotion—as was the case in the Merck and Pfizer cases—that arises from the fact that the allegedly improper conduct is not only regulated but also authorized by the FDA through the NDA process.¹⁴⁷ Basically, the FDA approved the labeling that the state attorneys general subsequently found insufficient. Opponents to the actions of the state attorneys general argue that public policy reasons favor a conformance between the states' enforcement of their consumer protection laws and the regulations enforced by the FDA.¹⁴⁸ The most persuasive reasons include: predictability for pharmaceutical companies that rely on the decisions of the FDA, uniformity between federal and state regulatory actions, and a general deference to the ability and authority of federal agencies involved in regulating prescription drugs.¹⁴⁹ Settlements under consumer protection laws could also be found to be preempted by federal law in the future, though this potential avenue may have been recently foreclosed.¹⁵⁰

Enhancing the FDA's ability to regulate prescription drugs after approval would serve to both restore the confidence of the state attorneys general in federal regulatory endeavors and simultaneously satisfy the important public policy concerns voiced by opponents to the state efforts.

III

A MORE TRUSTWORTHY AND EFFECTIVE FDA

For the FDA to truly perform effectively and decrease the regulatory void filled by the enforcement actions of the state attorneys general, important changes to the structure of the agency must be implemented. The FDA needs to be able to make educated decisions based on a more accurate accumulation of information detailing

¹⁴⁶ See Victor E. Schwartz et al., "That's Unfair!" Says Who—The Government or the Litigant?: *Consumer Protection Claims Involving Regulated Conduct*, 47 WASHBURN L.J. 93, 119 (2007).

¹⁴⁷ *Id.* at 94.

¹⁴⁸ See *id.* at 99.

¹⁴⁹ See *id.* at 94.

¹⁵⁰ Preemption issues involving these settlements were likely avoided due to the U.S. Supreme Court's decision in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009).

developing safety concerns with a particular drug. The decision-making responsibility within the FDA must be vested in the Office of Surveillance and Epidemiology, as opposed to the current system in which the Office of New Drugs makes postapproval decisions. This shift in responsibility will allow a single office within the FDA to focus solely on the postapproval regulation of drugs. That office will have both access to safety information and the ability to unilaterally make binding regulatory decisions based on that information.

A. Increased Specialization Within the FDA

The section of the FDA that is responsible for the efficacy and safety of prescription drugs throughout the drug's lifetime is the Center for Drug Evaluation and Research (CDER).¹⁵¹ Within the CDER, two distinct subunits play roles in the postapproval regulation of prescription drugs, namely the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE).¹⁵² The OND is responsible for both approving a particular drug and regulating that same drug based on postapproval safety data.¹⁵³ The OSE primarily focuses on the emerging safety data about prescription drugs by monitoring reported adverse events and participating in drug safety research outside of the agency.¹⁵⁴

Although the most knowledgeable about postapproval safety based on its information-gathering function, the OSE mostly serves as an advisory body to the OND. As the Merck and Eli Lilly examples demonstrated above¹⁵⁵, even a system that fully educates the FDA about the safety profile of a drug may be subject to inconsistent interpretations within the agency. For this reason and others, the decision-making responsibility following analysis of postapproval safety data must be vested in a subunit of the FDA that is only concerned with postapproval regulation. This office must be separate from its counterpart that is responsible for approving the drug for introduction into the market.

¹⁵¹ U.S. Food & Drug Admin., FAQs About CDER, <http://www.fda.gov/AboutFDA/CentersOffices/CDER/FAQsaboutCDER/default.htm#1> (last visited Mar. 17, 2010).

¹⁵² U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 54, at 4. The careful reader will notice that the report by the GAO refers to an Office of Drug Safety. Shortly after the GAO's report, the Office of Drug Safety was renamed the Office of Surveillance and Epidemiology.

¹⁵³ *Id.*

¹⁵⁴ *Id.* at 4–5.

¹⁵⁵ See *supra* notes 11–16, 22–26 and accompanying text.

Although the OND works closely with the OSE, the vesting of decision-making authority regarding postapproval regulation in the former presents significant difficulties. These problems include a lack of communication between the two offices concerning the final decisions made by the OND.¹⁵⁶ Frequently, the OSE does not even know what decision the OND has reached. In addition to the issues arising from the communication between these offices, there is an inherent conflict of interest that develops from vesting postapproval decision-making responsibility in the OND.¹⁵⁷ Requiring the office that initially approved the prescription drug to essentially discredit its own approval decision by actively trying to find safety and efficacy deficiencies almost necessarily creates an environment for substantial harmful biases.¹⁵⁸ This situation may have unwittingly played a role in the understating of the risks of Vioxx discussed above.

B. A New Office of Postmarket Drug Evaluation

The federal government can eliminate these issues and, thus, more effectively regulate prescription drugs in the marketplace by transforming the OSE into a pseudo-separate agency with the ability to make postapproval regulatory decisions and enforce those decisions. The OSE, or a comparable subunit within the FDA, could serve as a continuous “third-party” decision reviewer of the OND’s decision to approve a drug. This constant review would presumably be void of any conflict of interest, as the office, unlike the OND, would have no desire to “save face.”

This proposal is comparable to the failed Food and Drug Administration Act of 2005 (FDAA) that was chiefly sponsored by Senator Charles Grassley.¹⁵⁹ This bill sought to establish the “Center for Post-Market Drug Evaluation and Research” (Center) within the FDA as solely responsible for the effectiveness and safety of drugs in the marketplace.¹⁶⁰ To fulfill the new Center’s primary responsibility, the FDAA obligated the Director of the Center to

¹⁵⁶ *Id.* at 5.

¹⁵⁷ See Fontanarosa et al., *supra* note 3, at 2647.

¹⁵⁸ See *id.*

¹⁵⁹ AM. SOC’Y OF HEALTH-SYSTEM PHARMACISTS, THE FOOD AND DRUG ADMINISTRATION SAFETY ACT OF 2005—SUMMARY 2005, http://www.ashp.org/s_ashp/docs/files/GAD_GrassleyDodd_FDASASummary2.pdf. The bill never passed the committee review stage of the legislative process in the Senate during the 109th Session of Congress. *Id.*

¹⁶⁰ *Id.*

conduct postapproval surveillance of drugs and “take corrective action if a drug or biological product presents an unreasonable risk to patients or the general public.”¹⁶¹

To transform the powers and responsibilities of the OSE, a bill similar to the FDAA should be sponsored in the next legislative session with a few modifications. The FDAA gave the discretion to enforce postapproval regulations to the Secretary of the U.S. Department of Health and Human Services through the availability of civil penalties for violations.¹⁶² But this power is more appropriately placed in the hands of the newly proposed division charged with determining if additional regulation is even necessary. The effectiveness of new regulations and decisions regarding current regulations would likely depend on the ability of the new division to impose penalties for violations and, therefore, create proper guidelines for pharmaceutical companies to operate under.

In the context of Phase IV trials, this new division should be charged with the duty of requesting and ensuring that the pharmaceutical company sponsoring an NDA completes an appropriate Phase IV trial.¹⁶³ This division could overcome the “institutional risk-aversion that pervades the FDA” and create policies for conducting Phase IV trials that are clearly articulated to sponsors.¹⁶⁴ The new division should have the capability to enforce any Phase IV mandatory “requests,” through civil penalties or other actions, using federal law.

To remove some amount of discretion and uncertainty involved with Phase IV trial requests, Congress should consider making Phase IV studies uniformly mandatory for all prescription drugs that are approved, as recommended by various experts.¹⁶⁵ In fact, there have been recent efforts by legislators to pass laws empowering the FDA to demand postapproval investigations concerning substantial safety problems revealed by MedWatch, the system through which the FDA

¹⁶¹ *Id.* The Act also gave the Director of the Center the duties of determining when a postmarket study should be required; requiring the sponsor of such a drug or product to contract with domestic and international surveillance databases to perform any observational studies; determining whether a drug or product presents a serious risk to the health of the public; and providing timely information about safety and efficacy drugs and biological products to the public and health care providers. *Id.*

¹⁶² *Id.*

¹⁶³ This power is generally given to the Center by sections 2 and 3 of the failed Food and Drug Administration Safety Act of 2005.

¹⁶⁴ Steenburg, *supra* note 34, at 327.

¹⁶⁵ *See, e.g.,* Fontanarosa et al., *supra* note 3, at 2649–50.

gathers adverse event information, or other sources that monitor a drug's use.¹⁶⁶ These efforts seek to codify and strengthen the current system in which the FDA conditions drug approval on the "agreement" of the sponsor to conduct Phase IV trials.¹⁶⁷

For example, the recently enacted FDA Amendments Act adds to the ability of the FDA to utilize Phase IV trials. The FDA Amendments Act allows the FDA to compel sponsoring companies to conduct Phase IV trials as a condition of approval.¹⁶⁸ The Act also gives the FDA the power to require postapproval Phase IV trials if safety information shows a new safety risk is emerging from the drug's usage by the general public.¹⁶⁹ But in practice, once approval of the various drugs has occurred, the pharmaceutical companies routinely fail to fulfill their Phase IV trial promises.¹⁷⁰ The new division should be empowered to levy the appropriate civil penalties on a company that is not following the division's commands to perform Phase IV trials. This would enable a specific division of the FDA to monitor and accurately ensure a company's compliance with Phase IV study requests.

There is certainly a concern that emerges from this new division's solitary discretion, which could be overwhelmed by the lobbying efforts of the pharmaceutical industry. Merely empowering the new division to compel Phase IV studies would likely continue the perpetuation of uncertainty on the part of pharmaceutical companies—which will not be able to predict what amount of resources to budget for Phase IV trials.¹⁷¹ But, the responsive concern is the great deal of confusion currently resulting from FDA reviewers who admit they are often "unsure what types of [postapproval] commitments to request of sponsors."¹⁷² This issue could be cured by creating an official policy within the new division that sets a minimum or floor for postapproval studies based on the

¹⁶⁶ Affordable Health Care Act, S. 16, 109th Cong. § 507(a) (2005).

¹⁶⁷ Steenburg, *supra* note 34, at 333. The FDA arguably possesses unreviewable discretion in approving prescription drugs to be placed on the market, and thus, pharmaceutical companies may have no recourse for the FDA's "requirement" of a Phase IV trial. *Id.* at 334.

¹⁶⁸ Kessler & Vladeck, *supra* note 32, at 490.

¹⁶⁹ *Id.* at 491.

¹⁷⁰ Steenburg, *supra* note 34, at 337.

¹⁷¹ *See id.* at 341.

¹⁷² OFFICE OF INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUMAN SERVS., FDA'S REVIEW PROCESS FOR NEW DRUG APPLICATIONS: A MANAGEMENT REVIEW 19 (2003), available at <http://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf>.

class of the prescription drug. The level of mandatory postapproval scrutiny would be calculated relative to the potential safety issues involved with each class of drugs and the likely users in the class, if such a population can be determined. For example, sponsors of anti-inflammatory drugs could expect to, at a minimum, conduct a three-year Phase IV study of the safety and efficacy of the drugs when used by juveniles. The new proposed division could then raise the level of scrutiny needed based on the novelty of the class—a class of drugs that have been used by the public for decades would receive less scrutiny than a brand-new class.¹⁷³

With these powers, the new division would not experience the disabling disconnection currently encountered between the decision making of the OND and the suggestions of the OSE.¹⁷⁴ Further, this delegation of enforcement power would create a pseudo-agency within the FDA with similar powers to the state attorneys general, thereby creating a nationwide “watchdog” for postapproval prescription drugs. With a nationwide enforcer of the FDCA, the state attorneys general will likely not have to continue to perform a substantial regulatory gap-filling function. The American public would have an invigorated faith in the safety of the pharmaceutical products they use everyday.

CONCLUSION

The American public’s confidence in the FDA is waning in the midst of increased reporting of inefficiencies in the agency. The missteps by the FDA in the postapproval regulation of prescription drugs are magnified by the pervasive use of prescription drugs in the market. State attorneys general have responded to the public’s lack of confidence by bringing suit against pharmaceutical companies under state consumer protection laws. In protecting their citizens, the state

¹⁷³ There may be an issue with the discretion to raise or lower the minimum postapproval study that would be mandatory for a class. Although the new division within the FDA would be able to change the minimum based on the longevity of the class of drugs, adequate notice will have to be given to the pharmaceutical industry to allow for the adjustment of budgeted resources.

¹⁷⁴ There is certainly a valid argument that the separation of regulatory and enforcement powers between the FDA and the Department of Health and Human Services is necessary to add a layer of oversight to the entire process. However, this concern does not outweigh the interest in efficiency and reliability in the proposed regulatory scheme. The new agency will have the greatest understanding of the imposed regulation on the pharmaceutical company and thus should be empowered to enforce compliance with the agency’s decision.

attorneys general have begun to institute new regulations in the prescription drug industry through the use of innovative settlement terms. The state attorneys general have also used these settlement agreements to take a more active role filling the void created by an inefficient FDA.

But there are many difficulties that arise from a system in which two different enforcers are monitoring and enforcing a pharmaceutical company's compliance with federal law. Not the least of these problems is the likely overlap of penalties and inconsistent interpretations of the federal regulations by the two bodies.

To overcome these difficulties, the FDA should reorganize itself and push Congress for greater enforcement capabilities. The agency should vest the responsibility for monitoring and regulating prescription drugs after their approval to the Office of Surveillance and Epidemiology, or a newly created division. To ensure the new division can restore public trust in postapproval regulation of prescription drugs, Congress should enact legislation that allows it to effectively regulate through the use of civil fines and criminal prosecution against companies that refuse to follow its orders.

With this new division in place, the American public will be able to trust the FDA to accurately and neutrally evaluate both the safety and efficacy of prescription drugs even after the drugs have been approved for sale, and public faith in the agency will be restored.