Preemption, tort reform, and pharmaceutical claims

Part two: Has the Food and Drug Administration shown it is solely responsible for the protection of patients? Can it do so? Will it do so?

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There should be no question that adverse drug events are a significant issue. A recent report indicated that in 2005 there were 89,842 serious adverse drug-related events (1), and 15,107 of these adverse events were deaths (1). In 2002, adverse drug events were associated with more than 3 million hospital admissions and increased the US hospitalization bill by $17 billion (2). Non–hospitalization-related medication injuries cost $76.6 billion (2). Data show that 3% to 4% of medications are withdrawn for safety reasons (3). With facts such as these, it should be no surprise that adverse drug events are the most common iatrogenic cause of patient injury (4).

Traditionally, patients have been able to pursue legal action if they were harmed by a medication side effect about which they were not adequately warned (5). In such circumstances, patients have been able to pursue a "failure-to-warn" claim against the medication's manufacturer and/or the health care provider who prescribed the medication.

The pharmaceutical industry is currently pushing an agenda to essentially eliminate the ability of individuals to pursue failure-to-warn claims against manufacturers, regardless of the adequacy of the warning provided. Despite the existence of serious questions about the integrity of industry raised by misconduct involving the medications Ketek, Neurontin, Paxil, OxyContin, Trasylol, Vioxx, and Zyprexa, industry asserts with a straight face that because it is regulated by the US Food and Drug Administration (FDA), federal law should bar an individual's ability to bring a failure-to-warn claim. The concern is that some courts have begun to buy this argument.

Industry's argument is based on its contention that Congress intended the FDA to be solely responsible for policing and punishing manufacturer misconduct in the context of medication promotion, safety, and warnings. Recent judicial opinions have raised the very real possibility that pharmaceutical manufacturers may now be immune from failure-to-warn lawsuits in many states. If the dominoes continue to fall, the American public will be prevented from pursuit of failure-to-warn claims against a manufacturer or will be allowed to pursue such claims only when and if the FDA has expressly determined that a manufacturer acted fraudulently.

BACKGROUND ISSUE

As discussed in the October 2007 issue of *Proceedings,* the legal issue is preemption. In simplest terms, the question is whether or not the scope of regulation provided for under the Food, Drug, and Cosmetics Act (FDCA) is so persuasive that it indicates that Congress intended the FDA to have exclusive authority over regulation of medication warnings to the exclusion of state law provisions (6). If preemption exists, manufacturers are essentially immune from suit. Any claim based on state law would be barred. Since there is no federal cause of action for a manufacturer's failure to warn (7), an injured individual would have no right of recourse.

Prior to 2001, the pharmaceutical industry's attempts to convince courts that failure-to-warn claims were preempted by FDA authority under the FDCA met with little success (8). In 2001, a US Supreme Court decision based on a very narrow, specific, and unique set of facts provided industry with renewed hope and new authority on which to base a claim of preemption (9). This case, *Buckman v. Plaintiffs' Legal Committee,* was discussed in the last issue. In addition to *Buckman,* recent state tort reform legislation allowing failure-to-warn claims only if the FDA has been defrauded or misled has unwittingly provided industry with further ammunition on which to claim preemption. Then in 2006, the FDA took an about-face and came to industry's defense. Directly contradicting its prior, longstanding position on this issue, the FDA unilaterally proclaimed, without consulting with the individual states in apparent violation of a standing executive order, that it had the sole authority over medication warnings, to the exclusion of existing state law (10, 11). Fortunately, most courts have not been persuaded by that purely political, self-serving action. Legally, the focus is on congressional intent, not the desires of the current administration and its appointees (6).

In the last *Proceedings,* we analyzed and discussed application of these issues to the recent Texas *Ledbetter* decision, which favored Merck on a claim related to its former COX-2 inhibitor, Vioxx. In *Ledbetter*, a trial court in Houston, Texas, held that because the only practical manner in which a pharmaceutical company could be sued in Texas for failure to warn focused on an area in which there was federal regulation of the

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pharmaceutical industry, preemption existed and Merck could not be sued for a failure to warn under Texas law (12). Because there was no federal tort law in this area, Merck could not be sued on that basis and was entitled to dismissal of plaintiffs' failure-to-warn claims (12). Prescribing physicians, however, might not be entitled to those same protections (13), essentially placing them in the legal position of being insurers for the pharmaceutical industry.

In this issue, we analyze and discuss the policy underlying the preemption issues addressed in *Ledbetter* and similar cases. The primary policy underlying these decisions is the claim that the scope of federal regulation of the pharmaceutical industry under the FDCA indicates that Congress has charged the FDA with enforcement of industry conduct, that the FDA has enforced and will continue to enforce provisions of the FDCA that apply to medication warnings, and that the FDA has protected and will protect the American public from harmful medications, to the complete exclusion of any additional or different state law requirements. As such, all separate state law provisions that allow individuals to pursue legal action against pharmaceutical manufacturers are contrary to the provisions and purpose of FDCA, are an obstacle to congressional intent, and operate only to frustrate and interfere with the FDA's regulation of the pharmaceutical industry (6).

To evaluate this issue, we examine the FDA's enforcement powers, areas of concern raised about the FDA's ability to protect the public, recent data on FDA enforcement efforts, specific examples that highlight concerns about the FDA's ability to protect the public, and whether civil litigation has a constructive role in drug safety.

NEW DEVELOPMENTS

Before delving into these issues, a review of developments that have occurred since the first part of this article was published in October 2007 is in order. The Texas *Ledbetter* decision has been appealed by the plaintiff and is pending before the 14th Court of Appeals in Houston, Texas. The appellant's (plaintiff's) brief was filed with the court of appeals on October 18, 2007. Assuming there are no extensions, appellee's (Merck's) brief will be due toward the end of 2007.

In addition, the US Supreme Court will weigh in on the issue of preemption in this area. On September 25, 2007, the Supreme Court agreed to hear *Warner-Lambert & Co. v. Kent* (14). As discussed in the last issue, the Supreme Court has already agreed to hear the preemption issue raised in *Riegel v. Medtronic* (15). *Riegel*, however, is a medical device case involving application of different regulations and issues, which are not relevant to pharmaceuticals (16). In *Kent,* the Supreme Court will address the US Court of Appeals Second Circuit decision in *Desiano v. Warner-Lambert & Co.* In *Desiano* the Second Circuit ruled that failure-to-warn claims were not preempted in connection with utilization of an exception contained in Michigan's statutory provision granting pharmaceutical manufacturers immunity from suit in certain circumstances. Warner-Lambert claims that because the exception to immunity invokes FDCA provisions, state law claims are preempted and it cannot be sued. The US Court of Appeals for the Second Circuit disagreed with this argument and found no preemption (17). The Michigan statute at issue in *Desiano/Kent* is somewhat similar to the Texas statute at issue in *Ledbetter*, the primary difference being that the Michigan statute specifically incorporates federal regulations and grants manufacturers immunity from suit (18), while the Texas statute only provides a rebuttable presumption that the manufacturer's conduct was appropriate unless there was misconduct in its dealings with the FDA (19).

The Michigan legislature has also been at work on the immunity provision at issue in *Desiano/Kent*. Earlier this year the Michigan House of Representatives passed a bill to end the statutory immunity previously granted to pharmaceutical manufacturers (20). This legislation is currently pending before the Michigan Senate. It will be interesting to see what happens in Michigan and to see if the other few states with similar provisions address the fact that their own tort reform legislation may provide a basis on which pharmaceutical manufacturers can obtain complete immunity from failure-to-warn claims.

On September 27, 2007, President Bush signed the Food and Drug Administration Amendment Acts of 2007 (FDAAA) (21). The FDAAA provision primarily relevant to these issues involves renewal of and amendments to the Prescription Drug User Fee Act (PDUFA). PDUFA is legislation first passed in 1992, renewed in 1997, and modified in 2002. The primary focus of this legislation is to allow the FDA to collect fees from pharmaceutical manufacturers to help fund reviews of new medications. In exchange for fees from industry, PDUFA provides for shorter review times and a more predictable review process. Prior to 2002, PDUFA prohibited the FDA from dedicating any of the user fees from industry to improve postmarketing surveillance of medication side effects (22). In fact, the FDA wanted a portion of these fees to go to safety funding, but the pharmaceutical industry refused (23). The 2002 legislation, however, provided for "modest" FDA safety surveillance funding from these fees (24, 25).

When considering these issues, keep in mind that the legal arguments and decisions discussed in part one and in this article were in no way based on (or could even take into account) any aspect or provision of FDAAA. In fact, FDAAA is not relevant to the issue at hand. The issue is, always has been, and should continue to be whether or not Congress solely charged the FDA with the exclusive power and jurisdiction to regulate manufacturer conduct in this area, to the exclusion of state law (6). We will, though, briefly evaluate the effect, if any, of relevant FDAAA provisions to the issues discussed below.

FDA ENFORCEMENT POWERS

The FDA's enforcement powers come from the FDCA. In the area of medication warnings, FDA authority primarily arises from its power over product labeling, such as the information about products in the *Physician's Desk Reference* (26). The FDA cites its jurisdiction over the product label as a basis of its authority over all a manufacturer's medication-related promotional or informational efforts, including direct-to-consumer advertising and product-related scientific and educational information (26).

Day-to-day evaluation of manufacturer compliance with the FDCA rests with the FDA Office of Regulatory Affairs, which employs about one third of all FDA personnel. These individuals are located in more than 16 field offices spread across the United States. Staff in the Office of Regulatory Affairs are charged with ensuring that "the FDA's high public health standards" are implemented by industry. These personnel include consumer safety officers, scientists, and public affairs specialists (27).

In the area of labeling/safety, the FDA's primary enforcement tools are its ability to seek civil penalties (28), criminal penalties (29), and injunctions (30). Within the Civil Division of the US Department of Justice, the Office of Consumer Litigation (OCL) is responsible for enforcement of FDA consumer protection. Frequently, OCL cases are originally developed in FDA field offices, reviewed by FDA's central office, and then sent to OCL. OCL also has responsibility to enforce the consumer protection programs of the Federal Trade Commission, Consumer Product Safety Commission, and National Highway Traffic Safety Administration (31).

The FDA also has the ability to join *qui tam* proceedings. *Qui tam* proceedings are legal actions in which a private individual asserts a fraud claim on behalf of the US government against a manufacturer (32, 33). Primarily, these are claims brought by industry insiders or whistle-blowers with personal knowledge of the misconduct at issue. The incentive for a private individual to bring such a claim (and for lawyers to sign on to represent individuals in these claims) is the provision that the individual receives 15% to 30% of any settlement amount or award (33).

Logistically and procedurally, *qui tam* suits are unique. When suit is filed by the private individual, referred to as the relator, the matter is sealed. Thus, the "defendant"-manufacturer is not aware that the claim has been filed or even exists. The US attorney for the district in which the case is filed is made aware of the case when it is filed. The United States then has a period of time to determine whether or not it wants to join as a plaintiff and take over the case (32, 33).

Joinder into *qui tam* proceedings appears to be the FDA's preferred method of legal enforcement action in pharmaceutical matters. The *qui tam* process, however, is not a rapid manner in which to obtain a legal determination of misconduct by a manufacturer. In fact, quite the opposite appears to be the rule more than the exception. Many times these cases remain under seal, hidden from the public view for years (34).

The *qui tam* process may serve FDA and government purposes. In fact, many of the government's high-profile victories against the pharmaceutical industry have resulted from *qui tam* proceedings (35). *Qui tam* proceedings provide no benefit to individuals injured by industry misconduct. Not only does the very nature of the process hide the truth from the public for an extended period of time, but the length of the process itself makes it a virtual certainty that limitations will bar individual claims predicated on a finding of misconduct generated from such a proceeding.

AREAS OF CONCERN RELATED TO THE FDA'S PROTECTION OF THE PUBLIC

Criticism that the FDA and the current American drug safety system are unable to adequately protect the public health has been common throughout the first years of the new millennium (22, 36–38). Criticism has focused on the FDA's inability to timely detect and respond to safety-related issues and its failure to enforce manufacturer violations of the FDCA.

The former criticism is related to infrastructure issues, such as decision-making processes, proper staffing, and proper funding, in addition to an inability to force manufacturers to perform clinical studies after a medication is approved for sale. The latter concern is much more troublesome because it appears to reflect lack of unity of purpose as well as an underlying administrative or political bias against an aggressive enforcement posture.

Acceleration of the approval process provided for under PDUFA is a possible reason for recent drug safety problems. Concerns exist that PDUFA promotes hasty approval of medications and drains the FDA's already limited postmarketing surveillance resources (39). FDA employees admit that they have been pressured to approve or recommend medications about which they had safety, efficacy, or quality concerns; that they were not given enough time to properly perform "an in-depth, science-based review" of a medication; and that the emphasis was no longer on medication safety but rather on medication approval (22–25).

The 2004 withdrawal of rofecoxib (Vioxx) spurred renewed criticism of inadequate postmarketing safety surveillance and the FDA's failure to timely communicate safety concerns raised after medications reach the market (25). Absence of adequate postmarketing safety surveillance has been related to the FDA's inability to translate possible drug safety concerns into high-quality postmarketing studies (23). This may be because the FDA "lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues" (40). Regardless, both the Institute of Medicine and the Government Accountability Office reported that our current process for "identifying drug risks was greatly in need of repair" (41). That may be an optimistic view of the situation. Former FDA Commissioner Dr. Mark McClellan has claimed that the United States does not have an active drug surveillance system (37).

The Vioxx situation also brought to light concern that the FDA approaches safety issues in a backward, industry-first manner. According to FDA employee Dr. David Graham, part of the problem with Vioxx was that the FDA requires "complete certainty" of an increased risk from a medication before it will act (42). If that's true, Dr. Graham is completely correct in his assessment that this "standard does not protect consumers, is prejudicially favorable to industry and its financial interests, rewards drug companies for not aggressively pursuing safety questions, and guarantees that some drugs with major safety problems will be approved and, once approved, will remain on the market, even in the face of extensive patient harm" (42).

The Vioxx situation also brought to light an apparent schism between premarketing review and postmarketing surveillance, the two major branches of the Center for Drug Evaluation and Research (CDER), the drug safety section of the FDA (22, 23, 43). As mentioned above, there are concerns that CDER is focused more on getting products to market and less on the rigorous scientific assessment and evaluation of products, particularly once they are approved (22, 23, 41). There are also claims that the FDA is reluctant to "reverse" prior approval of a product when postmarketing concerns arise (44).

Most bothersome, especially in light of manufacturers' attempts to insulate themselves from civil liability (or predicate such actions on an FDA finding of misconduct), is the belief that the FDA does not readily prosecute manufacturer misconduct (24). In fact, it is claimed that the FDA rarely exercises its authority to remove a medication from the market for a manufacturer's noncompliance with labeling or marketing regulations (37). Even more disturbing are reports that FDA scientists have been prevented from sharing safety concerns with the medical community and the public (22, 25). For example, in 2004, the FDA barred one of its medical review officers from presenting to an FDA advisory committee his findings that a number of leading antidepressants might increase the risk of suicide in children (45). With an enforcement reputation like this, it is no wonder that the FDA is currently viewed as "timid and toothless" (25).

Dysfunction between the FDA and OCL is also a factor. On March 24, 2005, the Washington Legal Foundation wrote the Department of Justice to advise it of numerous concerns it had about OCL's ability to fulfill its duties with respect to FDA/FDCA enforcement. Included in this correspondence were the following concerns:

- "Medical product manufacturers have been reluctant to provide consumers with a full range of truthful information about their products."
- "OCL has failed to provide clear guidance and coordination."
- "Notably absent . . . are FDCA prosecutions based on improper promotion of FDA-approved products."
- "OCL traditionally has undertaken actions to enforce FDCA only in response to FDA requests. And enforcement actions against manufacturers of FDA-approved products based on their promotional activities has not been among the actions it traditionally has been asked to undertake by FDA" (46).

In looking for the root cause of the FDA's illness, there are claims that our inadequate safety surveillance system is the problem (36). The argument here is that public safety crises and inadequate enforcement occur because the FDA cannot detect safety issues in the first place (36). This is certainly a logical position.

Financial limitations have also been blamed for safety and enforcement concerns. There is no doubt that the FDA is significantly overmatched by industry in terms of structure, organization, and manpower (24). Further, claims that the FDA's emphasis is on drug approval over safety because CDER receives much of its funding from industry under PDUFA is also intuitively logical (23–25, 39, 41). In fact, the Government Accountability Office determined that PDUFA resulted in a shifting of FDA funds away from safety surveillance (23, 25). Similarly, the FDA's lack of enforcement has been blamed on a lack of finances (37).

While logical, these financial and infrastructure arguments may overlook the real root of the problem: upper-level FDA leadership. During President Bush's two terms in office, there has not been stable FDA leadership (25). Until Dr. Andrew C. von Eschenbach's confirmation in June 2007, Dr. Mark McClellan was the only confirmed FDA commissioner. Dr. McClellan only served about 16 months (25). While Dr. von Eschenbach's confirmation has now provided the FDA with a permanent commissioner, his appointment has not been without controversy (38, 47).

Controversy also surrounded President Bush's 2001 appointment of Daniel Troy as FDA chief counsel. This appointment was criticized because Mr. Troy had previously worked for private interests in fighting proposed FDA regulation of the tobacco industry and FDA efforts to restrict the promotion of medications for unapproved uses (25, 48).

Mr. Troy's tenure with the FDA was also controversial. First, Mr. Troy cut back on enforcement and made decisions about FDA action without input from FDA staff based on personal meetings with industry (49). Second, Mr. Troy's role in the filing of an FDA *amicus* brief in support of Pfizer, a former client, on a preemption defense it was asserting before the US Court of Appeals for the Ninth Circuit generated controversy. Investigation revealed that contrary to the FDA tradition of not filing *amicus* briefs unless requested by the court, Pfizer had solicited the brief through direct contact with Mr. Troy (48). Further investigation led by US Congressman Maurice Hinchley revealed that Mr. Troy and/or his firm had received close to $400,000 from Pfizer in the months preceding his appointment to the FDA (48). Many viewed Mr. Troy's actions as part of a concerted politically based effort to minimize drug company accountability (48). Mr. Troy has since resigned from the FDA and is apparently back representing industry in dealings with the FDA (48).

Conflict of interest concerns within the FDA are not new and are not limited to President Bush's FDA appointments. For example, in 1969, 37 of 49 high-level officials who left FDA moved immediately into high-level positions with companies they were previously charged with regulating (50). In 1975, the General Accounting Office reported that 150 FDA officials owned stock in companies subject to FDA regulation (50).

Whether explained by the absence of an adequate safety surveillance system, lack of finances, the current administration's perceived antiregulatory philosophy, or the absence of stable, independent leadership (25), the perception exists that the FDA has become an apologist for the pharmaceutical industry rather than a protector of the American public (49). The perceptions discussed above are certainly not those a reasonable individual would associate with an agency charged with the degree of exclusive, extensive power over the pharmaceutical industry claimed by those who advocate preemption. In fact, these perceptions no doubt reflect poorly on an

agency claimed to police industry and to be a protector of the American public.

DATA ON FDA ENFORCEMENT

Data on FDA enforcement support the concerns discussed above and raise serious questions about whether enforcement is a priority with the FDA. In June 2006, the US House of Representatives Committee on Government Reform—Minority Staff Special Investigations Division released *Prescription for Harm: The Decline in FDA Enforcement Activity* (51). The data gathered for this report indicated that since 2000, the number of warning letters issued by the FDA for FDCA violations had dropped over 50% and was at a 15-year low. This decline cannot be attributed to manufacturer compliance, since the number of violations observed by FDA agents during field inspections during this time frame has been relatively constant. This decrease also cannot be attributed to a decline in medication advertisements or complaints about false and misleading advertisements (51).

During this same time frame, the report found that the number of seizures of mislabeled, defective, and dangerous products had dropped 44% (51). The decrease in enforcement found in *Prescription for Harm* was related, at least in part, to FDA officials' routine rejection of enforcement recommendations made by their field staff (51). Further, when action was taken, the "delay" between the actionable conduct and FDA action progressively got longer (51).

While these numbers appear to show a significant decline in enforcement into the first half of this decade, some claim that FDA enforcement during this time was more of a "mixed bag" (52). Others assert that by 2005 the FDA had reversed its "long in decline" lack of enforcement and that enforcement now "loomed large" over industry (53). In contrast to a consensus that enforcement was down, the FDA claimed that during the fiscal years 1998 to 2002, it pursued an "aggressive enforcement strategy" (54). This position is contradicted not only by the data but also by the statements and actions of the FDA's chief counsel (49).

In preparation of *Prescription for Harm,* three independent experts were retained to comment on their views of FDA enforcement based on materials turned over to Congress. These individuals were Dr. Jerry Avorn, Dr. Michael Wilkes, and Sammie Young. Their assessments of the situation do not mince words.

Dr. Jerry Avorn is a professor of medicine at Harvard Medical School and chief of pharmacoepidemiology and pharmacoeconomics at Brigham and Women's Hospital in Boston. Dr. Avorn has served as an expert witness for claimants in legal proceedings, including failure-to-warn claims, against manufacturers. For example, he recently served as an expert witness for plaintiffs in the Vioxx litigation against Merck. In his report, Dr. Avorn commented that there was a "pattern of regulatory neglect in FDA's central office" and "an apparent reluctance of the agency's central offices to act on problems of drug safety or false promotion that had been identified by its own district offices" and that he was left with the "image of an organization unable or unwilling to do its job effectively" (55).

Dr. Michael Wilkes is a professor of medicine and vice dean of medical education at the University of California at Davis School of Medicine. Dr. Wilkes, while acknowledging that he may not have all the FDA data on enforcement during this time frame, wrote that he was concerned that central administration at the FDA "has systematically ignored District Field Officers and regularly overridden their explicit and well documented concerns about drug safety and public health." Dr. Wilkes also noted that there was a "large number of cases where CDER disapproved sending out a warning letter because CDER itself had missed an internal deadline" (56).

Sammie Young is a former FDA enforcement official. She retired from the FDA in 1992. Arriving at the same concerns as Dr. Avorn and Dr. Wilkes, Ms. Young stated that her review suggested "that FDA is not fully carrying out its mission of protecting the public health" (57).

The interesting thing about Dr. Avorn's and Dr. Wilkes' assessments is their apparent conclusion that the primary source of the problem is not finances or the safety surveillance system itself. Findings of "a pattern of neglect," "reluctance" to act on problems identified by field staff, and "regular" overriding of explicit drug safety concerns by central administration clearly point to the overall attitude and leadership of the FDA as the problem.

In July 2006, shortly after release of *Prescription for Harm,* the Union of Concerned Scientists released its Survey of FDA Scientists. Findings from this survey similarly implicate FDA leadership as a source of the FDA's problems. Less than half of the 988 FDA scientists who responded to this survey felt that "FDA routinely provides complete and accurate information to the public" (58). Similarly, less than half respected the "integrity and professionalism of FDA leadership" (59).

During this time, medication-related serious adverse events and deaths from prescription and over-the-counter medications rose from 34,966 in 1998 to 89,842 in 2005. Fatal medication-related events rose from 5,519 in 1998 to 15,107 in 2005 (1). While these increases may be related in part to greater numbers of medication users, it is hard to argue that the data do not show a serious problem. Again, regardless of the root cause, it is hard to argue with those who feel that the FDA was not doing its job.

EXAMPLES OF PROBLEMS

Specific examples of problems further flesh out the concerns raised by many. Concerns about the FDA not doing its job are certainly not new. In the 1980s, there was documentation that the FDA failed to require sponsors to show positive benefit-risk ratios, did not properly monitor clinical trials, did not enforce adverse reaction reporting requirements, and was not aware of important published studies on medications it approved (60). More recent situations involving the medications alosetron (Lotronex), aprotinin (Trasylol), cerivastatin (Baycol), and telithromycin (Ketek) provide excellent illustrations of the findings and opinions discussed above and further information to use in trying to locate the root cause.

Alosetron (Lotronex) was approved in 2000 for irritable bowel syndrome. It was withdrawn later in 2000 following

serious adverse events, including deaths. About a year later, the manufacturer sought to remarket alosetron. In April 2002, an FDA advisory committee recommended remarketing the medication but with the restriction that it could be prescribed only by physicians who had been trained and certified to use the medication. Later, when approved by the FDA, the training and certification requirement recommended by the advisory committee was watered down to a mere "self-attestation of qualifications." Former FDA official Dr. Paul Stolley, who was with the FDA from 2000 to 2001, claims that the FDA priority was not safety but getting the medication back on the market. As examples, Dr. Stolley cited the fact that a senior FDA drug safety expert was told not to work on alosetron and that staff concerned about the medication were told to "help get this drug back on the market." Based on these facts, Dr. Stolley concluded that the FDA had become a servant of industry (61).

Aprotinin (Trasylol) is used to reduce perioperative bleeding. The concerns surrounding aprotinin came from two postmarketing studies that indicated that the medication could cause renal failure, stroke, and death (62). These concerns had not been raised by prior studies (63). In response to this development, the FDA convened an advisory committee meeting. Aprotinin's manufacturer submitted a safety analysis to the advisory committee for review but failed to disclose or include findings by a private research organization it hired to study postoperative complications. Data from this work supported postmarketing concerns that the medication posed significant risks to patients (62, 63). Essentially, the manufacturer "hid" this unfavorable data from the FDA. This same manufacturer had previously been accused of hiding unfavorable data in connection with another medication, cerivastatin. To date, however, there has been no claim or attempt by the FDA to establish manufacturer wrongdoing in either of those situations.

Telithromycin (Ketek) is an antibiotic used to circumvent antibiotic resistance. The concerns with telithromycin centered on liver injury. The process surrounding approval of this medication was fraught with trouble. First, fraud was discovered in connection with the enrollment of patients for a preapproval clinical trial. In addition, FDA inspection of the clinical trial sites obtained information that raised serious concerns about the integrity of the trial. In fact, 4 of the 10 inspected sites were referred for criminal prosecution, and one physician was sentenced to 57 months of federal prison time for her actions (64).

Despite these significant issues, data from this study were submitted to the advisory committee charged with evaluating telithromycin. Within this submission, there was no mention of concerns about the study or the integrity of the underlying data. Unaware of these issues, the advisory committee recommended approval of the medication. Next, FDA postmarketing evaluation of the safety of the medication was performed using only the manufacturer's postmarketing data (which is extremely unusual because these data are generally felt to be unreliable). In connection with this postmarketing safety evaluation, contrary to FDA policy, the FDA did not require the manufacturer to verify the accuracy and completeness of that data. Further, the FDA did not follow recommendations to investigate records from the fraud-fraught clinical trial to see if the manufacturer was aware of the underlying fraud when those data were submitted to the FDA (64).

In April 2004, telithromycin was approved for marketing by the FDA. Again, contrary to FDA policy, approval was not based on clinical trial data showing efficacy. Soon thereafter, there were reports of medication-associated liver injury. Despite alerts to senior FDA management, the FDA took no substantive action. In fact, reviewers at the FDA were instructed by the then-acting Commissioner von Eschenbach to not discuss issues related to the medication outside of the FDA. It was not until 16 months after the public first report of liver failure that the FDA relabeled telithromycin to include the risk of severe liver toxicity (64).

In addition to these examples is the well-known Vioxx situation. Vioxx is often used as the primary illustration of FDA failure to protect the public (41, 42, 65, 66). Vioxx is cited as evidence that FDA is too "passive" in its approach to safety and that the FDA fails to heed "warning signs." Given such institutional inertia, there was an almost 2-year delay in label revisions to reflect the cardiovascular risks associated with Vioxx (66). While some claim that Vioxx is really a regulatory success story because the process resulted in an increase in our knowledge about the safety profile of COX-2 inhibitors (67), the consensus appears to be that Vioxx was a "drug disaster" that will not be repeated (39, 41, 42, 65, 66).

These examples give further support to those concerned about FDA leadership. They provide specific instances in which the FDA has sided with industry, given a higher priority to drug approval than drug safety, and taken a rather lax attitude toward enforcement related to potential industry wrongdoing.

DOES CIVIL LITIGATION HAVE A CONSTRUCTIVE ROLE IN DRUG SAFETY?

Current wisdom appears to be that products liability claims serve no legitimate purpose in promoting drug safety. This view is probably best evidenced by the numerous state-specific tort reform measures that have been enacted during the past few years, including the statutes discussed in this article and the last article (18, 19). It is naive, however, to simply accept that litigation is part of the evil and to expect that tort reform and the FDAAA will somehow reverse the FDA's and industry's ills, particularly given the opacity of drug safety and legitimate concerns about FDA leadership.

The pharmaceutical industry, and regulation of that industry, is not a transparent process where drug safety is concerned. The FDA is no longer viewed by many as an independent evaluator in this process. In all fairness, that perception may simply be a function of FDA authority. The FDA does not perform its own studies. It relies on study information submitted to it by the pharmaceutical companies, as well as published medical studies and evaluations. As such, situations can occur in which the FDA is unaware of safety concerns because important information was not provided by the manufacturer (62) or was "hidden" by the manufacturer within the material provided (68). Thus, even

if concerns about the FDA's relationship with industry under PDUFA (25, 49) and about relationships between advisory committee members and industry (69) are set aside, the truth is that the FDA cannot be considered an "independent" source of information about medications. The most that can be said is that the FDA is another reviewer of existing information about a medication.

While some claim that the Freedom of Information Act provides transparency to this facet of the pharmaceutical industry (24), the unwieldy nature of the information request process, the highly scientific nature of the information available, and the voluminous nature of information involved provide the American public with little practical access to drug safety issues. For these reasons, any transparency must come from other sources.

In direct-to-consumer advertisements, the public is told to "ask your physician" for information about medications. While such a statement may appear to direct patients to an independent source of information, that is not necessarily the case. Physicians are not free from industry influence. It is true that physicians receive information on medications from numerous sources. In addition to direct contact with industry sales representatives, these sources include the *Physician's Desk Reference,* medical publications and references, continuing medical education seminars and materials, and manufacturer-sponsored programs.

While these sources of information may appear to be disinterested on the surface, they are frequently the subject of significant manufacturer influence. The *Physician's Desk Reference* information is simply the product label. This information is subject to FDA direction and approval, but the contents on the label are the result of negotiation and not FDA demands (39). Medical publications are not necessarily free from industry influence either. Manufacturers develop publication plans for most of their actively promoted medications. This plan often includes significant input from private medical research organizations. Such organizations are often involved in targeting authors and journals for articles that promote or support the use of a medication. The manufacturer and the medical research organization are also often involved in the editorial process. Sometimes an employee of the manufacturer is even one of the article's authors. Further, there have been accusations and evidence that some manufacturers and medical research organizations may have been the authors of "ghost-written" medical articles (70).

Manufacturers are also often involved in medical continuing education seminars. This support, however, is frequently in the form of an unrestricted monetary grant. While manufacturers may not have direct input into the presentation made at the seminar, they are frequently involved in the selection of the presenters for programs. It is not unusual for the presenters to be members of manufacturer-sponsored groups such as a speaker's bureau or advisory group. Similarly, manufacturers provide grants to specialty professional medical organizations (for example, the American College of Obstetricians and Gynecologists) to provide "disease process" education. This "disease process" education informs physicians about medical problems that can be treated by that manufacturer's medication(s). For example, a manufacturer who makes female hormone replacement products might sponsor educational programs about the "disease" of menopause, dangers it poses such as osteoporosis, and how certain classes of medications, such as estrogens, will treat this problem. These are marketing efforts pure and simple. Why else would manufacturers allocate significant financial resources to these efforts?

Television and print media are probably the primary day-to-day sources of public information on medications. There is not a single prime-time television program that you can watch or a single magazine or newspaper that you can read that does not have at least one "ask your doctor about" promotional piece. All of that information comes direct from the manufacturer. While this information and many of the other actions by industry discussed above are technically subject to FDA review and regulation (26), these promotional pieces and other information are generally not vetted by FDA before use. Further, there are concerns that FDA review of direct-to-consumer communications is inadequate and enforcement is lacking (71). For example, in 1997, the FDA sent manufacturers 142 letters notifying them of drug advertising violations. Only 21 such letters were sent in 2006 (71), about an 85% drop.

Other than this direct-to-consumer advertising, the other primary media source of pharmaceutical information is litigation-related news, whether it is investigative reporting, updates on evidence and testimony, or news about settlements and verdicts. Even litigation, however, has limits. While review of this information may appear to the uninformed to be a "tell-all" about drug safety issues, nothing could be further from the truth. In legal proceedings involving a medical product, the pharmaceutical manufacturer uniformly moves for and receives a cloak of secrecy covering the relevant facts in the form of protective and confidentiality orders. These orders cover at least all documents produced by the manufacturer and testimony from that manufacturer's employees.

While some may believe that complete transparency results when one of these cases goes to trial, that is not true either. At trial the only materials and testimony that become "public record" are the materials and testimony the trial judge feels are relevant to the specific claim before him. Volumes of information are frequently kept out of the "public record" of these proceedings on the basis that they cannot be directly linked to the time frame the medication was taken, the prescribing physician(s), and/or the injury at issue in that specific matter.

Even the attorneys and expert witnesses for all sides involved in these matters are prevented from disclosing substantial amounts of information to the public. The protective and confidentiality orders discussed above restrict what they are able to disclose to the public. Medical authors with knowledge of this confidential information must exercise care that their personal publications on related matters do not contain information from confidential company documents (72). Manufacturers closely and aggressively guard the "confidential" nature of these materials and make every effort to keep these materials out of

the public view (73). Unknown to the public, there are literally hundreds of Upton Sinclairs throughout the United States, but not one of them has the ability to publish their version of *The Jungle*, using specific facts as examples, as to the pharmaceutical industry. Opinions and examples must come from information of public record. Numerous relevant facts must be excluded.

There is no question that litigation-generated information is often sensational and subject to the self-interest of those that promulgate it. It is, however, a source of information that has eluded manufacturer suppression. Since complete reliance on industry for disclosure of information about its products is not seen as a prudent practice (67), doesn't litigation-generated information serve some purpose? In the absence of litigation-generated scrutiny, where is the public to look for "balance," particularly if FDA leadership is focused on drug approval and not drug safety or enforcement?

The concerns and data discussed above certainly support contentions that the FDA has been unable and/or unwilling to police industry in an effective manner. The fact that the FDA recently proclaimed itself as the sole arbiter of manufacturer conduct, to the exclusion of state law (10, 11), gives further support to those who believe that the FDA's current industry-friendly posture exists and is policy of the current administration. This sentiment is further bolstered by the fact that prior to that declaration, the FDA took the position that state law requirements on industry were in addition to and consistent with FDA requirements and that FDA regulations placed only minimum requirements on industry (10, 74). Given this about-face by the FDA, judicial views that state law products liability claims provide an "important backstop to the federal regulatory scheme" may be more accurate than we would want to admit (75).

The medical profession has also acknowledged that litigation may provide a beneficial contribution to drug safety. The drug litigation has "revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior" (76). In addition, information learned from litigation has revealed weaknesses in the regulatory process itself, such as manufacturers' ability to suppress or hide adverse event data (76). The importance of this contribution cannot be overlooked, since many of these issues have been addressed in FDAAA.

It is true that the litigation process is subject to abuse, that is has been abused by some and will continue to be abused by some. Aside from the underlying legal issue, the question that we need to ask ourselves is whether or not the wholesale elimination of private individual lawsuits against manufacturers is what Congress intended under FDCA and, more importantly, whether it will improve drug safety. Given the recent significant concerns of manufacturer misconduct related to the conduct of clinical trials (Ketek [64]), reporting of clinical trial adverse event data to the FDA (Paxil [76, 77], Rezulin [76], Vioxx [76]), reporting of postmarketing trial and adverse events data to the FDA (Baycol [62], Trasylol [62, 63]), improper promotion of medications (Neurontin [78], OxyContin [79, 80], Vioxx [62, 66, 76, 81, 82], Zyprexa [77]), and failure to adequately report medication dangers to the public (OxyContin [79, 80], Vioxx [62, 66, 76, 81, 82], Zyprexa [76, 77])—all of which occurred in spite of the additional deterrent of private litigation—how could one reasonably posture that drug safety would improve in the absence of litigation and that litigation has frustrated the FDA's ability to regulate industry?

In considering this point, it is interesting to note that products liability litigation is not cited as a potential cause of the FDA's ills or our current drug safety problems. Given the FDA's recent attitude and track record, no one can credibly argue that the FDA is solely charged with policing the pharmaceutical industry. Further, it does not take a leap of faith to conclude that the absence of litigation will not increase drug safety. In fact, it would likely do nothing other than increase our risk of drug safety problems in the future.

DOES THE FDAAA ADDRESS THESE CONCERNS?

Key provisions of the FDAAA as they relate to PDUFA include additional safety surveillance funding; additional requirements regarding clinical trial data reporting; additional authority to require compliance with FDA-requested postmarketing studies and label changes; conflict of interest provisions; and creation of the Reagan-Udall Foundation to benefit product development, innovation, and safety (83). Thus, Congress has tried to address a number of the concerns we have discussed.

These new changes, without question, "are important steps" in the right direction (84). While better tools to ensure the safety of the American people may be on their way to the FDA, it is much too early to declare the patient cured, to claim that the American public is now magically protected, or to assert that we should now suddenly have unquestioned confidence in the FDA. It is not as if the FDA had no enforcement tools prior to September 27, 2007. Statutorily, the FDA has had the long-standing ability to seek civil penalties, criminal penalties, and injunctive relief for violations of the FDCA (28–30). In fact, prior to September 2007, the FDA had the ability to remove medications from the market if manufacturers did not comply with its marketing or labeling recommendations. The issue has not been a lack of tools; it has been a lack of willingness to use the tools available (37).

It is not surprising that the medical profession and Americans generally do not have confidence in the FDA (25, 37, 42, 85). Many reasons for this sentiment cannot be addressed by any legislation. They must be addressed by FDA leadership and those responsible for selecting FDA leadership. Until the FDA addresses these concerns and unequivocally reclaims the public's confidence, it should not be trusted to be the sole arbiter of industry conduct, no matter congressional intent or the authority provided under government regulations.

One problem the FDA needs to address is its central office's lack of action on the findings and recommendations of FDA scientists and staff. It has been reported that the central office does not act on violations found by staff (51) and suppresses drug safety questions raised by FDA scientists (25, 42, 45). It is no wonder that the morale of FDA scientists and staff is poor (58, 59). If this attitude persists, FDAAA's lauded drug safety

provisions cannot be expected to have a significant effect on drug safety. Until the FDA central office displays confidence and trust in the integrity of its scientists and staff and demonstrates a better commitment to their judgments and recommendations, morale will continue to be poor and the FDA will not attract or retain quality scientists and staff.

Another problem is the FDA's lack of commitment to regulatory enforcement (24, 49, 51). Worrisome is the fact that this perception is supported not only by data (51) but by statements from FDA leadership (49). The fact that FDA-OCL enforcement efforts are not effective (46) and that the FDA frequently elects to "enforce" its regulations by joining private individual-initiated *qui tam* suits only provides additional evidence to support the data and statements that the FDA has no institutional dedication to enforcement. Unless the FDA is committed to enforcement, the additional enforcement powers granted by FDAAA will simply gather dust and will have no effect on drug safety.

The FDA's approach to safety issues is another problem. When safety concerns are raised, rather than requiring "complete certainty" that a medication is safe and effective, the FDA has utilized an industry-friendly standard of requiring "complete certainty" of an increased risk before acting (42). Reason would dictate that as the guardian of the public, the FDA's mindset should be, as suggested by FDA scientist Dr. David Graham, "patient safety rather than corporate profitability" (42).

The matters mentioned above are all rooted in and reflect the attitude of top FDA officials and the individual or individuals involved in appointing those officials. Unfortunately for the FDA, these key leadership positions are political appointees, not internal, merit-based choices. The absence of stable leadership since 2000 has undoubtedly been a partial contributor to the concerns discussed above, since the absence of stable leadership can result in the lack of a consistent commitment to purpose. The information reviewed above, however, implicates the attitude reflected by FDA's appointed leaders during this time as the more likely explanation, primarily because top leaders have been the ones who have not followed through on the findings and recommendations of subordinates and because of the actions and statements of those leaders (49). Further, it is probably not coincidental that many of the specific instances that have brought concerns about the FDA to the public have occurred during this same time frame.

While the FDA now has a confirmed commissioner, it is too early to tell if he brings a new attitude to the FDA or if the FDA will still be an apologist for industry, not a protector of the public. While Dr. von Eschenbach was easily confirmed, concerns were raised about his lack of "cooperation" with Congress in its investigation of concerns surrounding the approval of Ketek (86). More recently, Dr. von Eschenbach overruled the almost unanimous recommendation of both internal FDA and outside scientists about the safety of emergency contraception (the morning-after pill) (87). Thus, worries that the FDA still serves a political agenda, skepticism about the ultimate effect of the FDAAA, and belief that the "new boss is the same as the old boss" in favoring industry over the public are justified. The FDA has fence-mending to do with the public, and it must start now.

WHAT ABOUT PREEMPTION?

Some may consider these issues a digression from the underlying issue of preemption. Not true. As discussed in part one of this article, a significant legal dispute exists over whether Congress really intended for the FDA to be the sole watchman over industry's drug safety responsibilities. As discussed in the last issue, it is only recently that the FDA has made this claim itself and only recently that preemption in this area has been favorably received by courts. Prior to recent rulings, there was no preemption in this area.

The information reviewed here only serves to illustrate that the FDA's own actions certainly do not reflect what one would expect to see from the sole arbiter of reasonable industry conduct. A perfect illustration of this point is the relation of recent cutbacks in enforcement to the feeling that there was too much FDA enforcement (49). Whether or not that was true at the time, it appears that the pendulum has swung and that legitimate concerns exist about inadequate enforcement.

If exclusive FDA enforcement was Congress' intent, we should be very worried. The facts show that the FDA is currently not up to this task, particularly when litigation is cited as providing significant contributions to drug safety (76). In fact, even a former high-ranking individual within the pharmaceutical industry has recognized that the FDA has not yet realized its potential as both the protector and promoter of public health (24). While FDAAA is a positive step, it cannot cure the FDA's ills. The FDA must earn back our trust with its own action. Enforcement powers and safety tools mean nothing absent a top-to-bottom institutional commitment to use those tools to protect the public.

While there are two sides to every issue, the well-published concerns about the FDA and its ability to protect the American public should cause any reasonable person to question the current premise behind preemption. Who is the FDA's "client"? If the FDA's "client" is industry, how can it realistically police industry and protect the public? If the FDA cannot identify safety issues, how can it enforce regulations related to drug safety? If the FDA does not follow its own regulations, how can we expect it to make industry do so? If the FDA has no real interest in enforcement, how can it be trusted to enforce its regulations? If the FDA has not shown that it can and will accept its exclusive enforcement role, why should there be blind acceptance that this duty is being and will be fulfilled? The FDAAA may very well be the first step towards providing the American public with more cost-effective, safe medications. Prudence and the FDA's track record require that we get answers to these questions before we, our government, and our courts give any consideration to the elimination of failure-to-warn claims by individuals against pharmaceutical manufacturers. Absent unequivocal answers to these and other questions that show that the FDA's primary goal is the protection of the public, complete reliance on the FDA to police the pharmaceutical industry and protect the American public is a foolhardy proposition.

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