"The Fox in the Chicken Coop"
FDA's Recent Intervention in Pharmaceutical Litigation

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It is error alone which needs the support of government. Truth can stand by itself.

—Thomas Jefferson

An alarming new trend has begun in pharmaceutical litigation. The FDA has recently taken the remarkable step of intervening in private civil litigation on behalf of defendant drug companies and against plaintiff consumers. The FDA is arguing that plaintiffs' claims that a drug manufacturer has failed to warn or has advertised a drug in a false and misleading manner are preempted because, if the package insert or advertisement passes FDA muster, no one should question its authority. In short, "because the FDA said so."

The FDA has recently intervened in three key cases. The first occurred in March 2002, on the eve of oral argument in the California Court of Appeals, wherein the United States appeared as amicus curiae on behalf of the defendants in *Dowhal v. SmithKline Beecham Consumer Healthcare*, a citizen suit backed by the California Attorney General which protested the defendants' failure to abide by California's Proposition 65 reproductive toxicity warning requirements in the labeling of their over-the-counter Nicotine Replacement Products. The FDA's position there was that the plaintiff's claims directly conflicted with FDA's determination that the Prop 65 warnings would render the products misbranded under federal law. The FDA stated that its determination was preemptive, even though the Modernization Act included an exclusionary provision to preemption for Prop 65 (due to the misbranding issue). FDA argued that liability in the *Dowhal* case would seriously undermine its efforts to encourage consumers to quit smoking.

In a July 12, 2002 opinion, the California Appellate Court, reversed summary judgment in favor of the defendants. The court found that the savings clause in the federal preemption provision, which explicitly provided that the law did not preempt Prop 65, was controlling, even where Prop 65 and the federal law were in direct conflict.

On October 23, 2002, the California Supreme Court accepted the defendants' petition for review. Such groups as the Pharmaceutical Research and Manufacturers of America, Consumer

Healthcare Products Association (CHPA), the Cosmetic, Toiletry, and Fragrance Association, and Grocery Manufacturers of America urged the California Supreme Court to review the lower court's decision. The defendant's brief was due on January 21, 2003.

In August 2002, the FDA intervened in a second case, *In Re Paxil Litigation*, a class action pending in the United States District Court, Central District of California, wherein the plaintiffs argue that the manufacturer, Glaxo SmithKline (GSK) failed to warn that Paxil causes withdrawal and dependence in patients who attempt to discontinue or taper off the drug. Last year, the plaintiffs filed a motion for preliminary injunction to stop GSK from making statements in its advertisements that Paxil is "non-habit forming." The district court initially granted the motion for preliminary injunction, however, after the FDA intervened, the court reversed its ruling. Despite its change of heart, the district court rejected GSK's and the FDA's federal preemption arguments:

> If anything, FDA's and GSK's arguments run contrary to the grain of other decisions.
>
> . . . FDA's . . . position vitiates, rather than advances, the FDCA's purpose of protecting the public. That is, FDA and GSK invite the Court to find that in enacting the FDCA for the purposes of protecting public health, Congress not only declined to provide for a private cause of action, but also eliminated the availability of common law state claims. This position contravenes common sense . . . and the Court declines the invitation.

Following the Court's order denying the preliminary injunction, FDA Chief Counsel, Daniel Troy stated in an interview with the *Boston Globe* that "the FDA agrees with [GSK's] allegation that Paxil is not habit-forming. The drug does not cause *withdrawal symptoms*, but causes a 'discontinuation syndrome.'" This statement seems ridiculously contrived when compared to the language found in foreign labels for Paxil, where GSK itself acknowledges that Paxil causes *withdrawal*:

Italy

> *Withdrawal* symptoms may occur if treatment is discontinued abruptly. Such symptoms . . . include: insomnia, dizziness, sweating, palpitations, nausea, anxiety, irritability, parasthesia and headache.

UK

> *[W]ithdrawal* symptoms have been reported on stopping treatment. . . . Dizziness, sensory disturbance (e.g., parasthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion have been reported following abrupt withdrawal of "Seroxat" [Paxil].

Ireland

> *Withdrawal* reactions have been reported following discontinuation of "Seroxat" [Paxil], these include dizziness, sensory disturbance (e.g., paraesthesia), anxiety, sleep disturbances (including intense dreams), agitation, tremor, nausea, sweating and confusion.

Netherlands

> [A]brupt discontinuation of Seroxat therapy must be avoided as this may result in *withdrawal* symptoms such as sleep disturbances, sensory disturbances, dizziness, agitation or anxiety, sweating and nausea.

Spain

> *Withdrawal symptoms[.]* Discontinuation of paroxetine administration (especially if it is abrupt) may lead to withdrawal symptoms such as dizziness, sensory disturbances (including paraesthesia and sensation of cramps), headache, sleep disturbances, agitation or anxiety, nausea and sweating.

Less than a month after its *In Re Paxil* intervention, the FDA intervened (in September 2002) in yet a third case. *Motus v. Pfizer* is a Zoloft suicide case currently on appeal in the Ninth Circuit. The plaintiff appealed the ruling by the district court granting defendant's motion for summary judgment on actual causation. (The district court found that an adequate warning would have made no difference because the prescribing physician did not read the label prior to prescribing the drug.) Pfizer, the manufacturer of Zoloft, cross appealed an earlier order by the district court denying its motion for partial summary judgment on federal preemption grounds.[1] The FDA filed an amicus brief with the Ninth Circuit and, without submitting any evidentiary material whatsoever, went so far as to state that "[a]ny warning that suggested a causal relationship between Zoloft and suicide would have been false or misleading and would have misbranded the drug in violation of federal law."

This is incredible given that Pfizer has never requested a label change. The FDA cannot possibly determine that a warning would constitute misbranding when it has not been presented with the reasons for the proposed label change. The FDA simply cannot make such a bold statement in a vacuum. Notwithstanding, the FDA's own regulations expressly provide that a drug company can add or strengthen a contraindication, warning, precaution, or adverse reaction without prior FDA approval.[2]

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[1] *See* Motus v. Pfizer, 127 F. Supp. 2d 1085 (U.S.D.C., C.D., Cal. 2000.)

[2] *See* 21 C.F.R. § 314.8(d).

Although it is highly unlikely that Pfizer would voluntarily seek a label change, it could easily do so based on the studies, documents, and testimony of its own employees and experts obtained in the *Motus* case. Indeed, there is more than sufficient evidence to establish a "reasonable possibility" of an association between Zoloft and suicide to require a label change.[3] In fact, two

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[3]For instance, a Pfizer physician, in response to a Rule 30(b)(6) deposition notice, testified on Pfizer's behalf, that Zoloft induces akathisia, a neurological phenomenon with characteristics of intense internal restlessness, agitation and dysphoria, and which is a known precursor to suicidality:

> Q. Is akathisia also known as hyperkinesia?
>
> A. Yes.
>
> Q. And both akathisia and hyperkinesia are considered extrapyramidal symptoms or disorders?
>
> A. Yes. Akathisia is considered an extrapyramidal symptom or disorder, as is hyperkinesia. But, again, there could be other causations. These terms are also similar to agitation, psycho motor agitation. It often could be very difficult to tell the difference between.
>
> Q. Do you agree that Zoloft can cause some people to experience akathisia or hyperkinesia?
>
> A. Yes.
>
> Q. How long has that been established, to your knowledge?
>
> A. I'm sure there were reports of the initial clinical trials of the depression database, depression studies that were occurring back in the 1980s.

The fact that Zoloft causes akathisia was also confirmed by another Pfizer scientist, Dr. Roger Lane, who, until early 2001, was the Medical Director of the Zoloft Product Strategy Team at Pfizer. Dr. Lane wrote two peer-reviewed articles on the subject of SSRI-induced akathisia. The first, published in 1995 is entitled: *The SSRIs: Advantages, Disadvantages and Differences.* In the article, Dr. Lane states:

> The SSRIs may influence dopamine neurone firing in the substantia nigra through their effects on serotonin input to this nucleus. *Therefore they can cause extrapyramidal side effects* (Baldwin, Fineberg and Montgomery, 1991). *The most common are akathisia . . . .* (Emphasis added.)

The association between akathisia and suicidality and its implications is, perhaps, best expressed in a later article by Lane published in 1998, *SSRI-Induced Extrapyramidal Side-Effects and Akathisia: Implications for Treatment:*

> It may be less of a question of patients experiencing [Prozac]-induced suicidal ideation, than patients feeling that "death is a welcome result" when the acutely discomforting symptoms of akathisia are experienced

recent analyses of the FDA's data by two separate groups of scientists raises serious concerns over the FDA's conclusions about the safety and efficacy of SSRIs.[4]

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on top of already distressing disorders.

Even the most generally recognized and accepted source for diagnosing mental disorders, the American Psychiatric Association's "Diagnostic Statistical Manual" of Mental Disorders (DSM), the current version of which is DSM-IV TR, acknowledges an association between SSRIs, akathisia, and suicide. The DSM-IV TR text referring to SSRI-induced akathisia states, under "Neuroleptic-Induced Acute Akathisia, Differential Diagnosis":

> *Serotonin-specific reuptake inhibitor antidepressant medications* [such as Prozac, Zoloft, Paxil] may produce akathisia that appears to be identical in phenomenology and treatment response to Neuroleptic-Induced Acute Akathisia. Akathisia due to nonneuroleptic medication can be diagnosed as *Medication-Induced Movement Disorder Not Otherwise Specified.* Other situations that might be included under Medication-Induced Movement Disorder Not Otherwise Specified are acute akathisia with only subjective or only objective complaints, but not both; . . .
>
> The subjective distress resulting from akathisia is significant and can lead to noncompliance with neuroleptic treatment. Akathisia may be associated with dysphoria, irritability, aggression, or suicide attempts.

Even Pfizer's own expert witnesses have acknowledged an association between akathisia and suicide:

> Q. Do you believe that akathisia precipitates suicide in some people?
>
> A. I believe that *akathisia is a risk factor for suicidal behavior.* Another witness (for Eli Lilly in a Prozac-induced murder/suicide) testified that akathisia "creates a state of severe anxiety which can exacerbate preexisting proclivities, tendencies, in an individual to engage in either suicide or violence. . . . Akathisia is a state of extreme anxiety. Anxiety in an individual who is predisposed to suicide can increase the risk of suicide, that's correct. Anxiety in the case of someone who is contemplating violent actions or who is prone to violent actions can lower the threshold for engaging in violent actions."

This does not even take into account the confidential internal Pfizer documents and studies that demonstrate that Zoloft can induce suicide in a percentage of patients.

[4]Dr. Arif Khan of the Northwest Clinical Research Center in Bellevue Washington, in August 2002,

> reported an analysis of clinical trial data for drugs approved by the Food and Drug Administration between 1985 and 2000. This included suicide and attempted suicide rates for more than 71,604 patients treated with the atypical antipsychotics . . . and . . . all the selective serotonin reuptake inhibitors . . . and [an] anticonvulsant.

We have been asked by many: "Why is the FDA all of a sudden getting involved in these cases?" It has become abundantly clear to us that the current political climate within the FDA is the cause of this brazen new stance.

In fact, behind each of these FDA interventions is FDA Chief Counsel, Daniel Troy, appointed by President Bush in 2001.

> One striking finding was the elevated rate of completed suicides for patients during these trials. Compared with the rate of 11/100,000 persons per year for the population at large, the rates of completed suicide were 752/100,000 persons per year for those in antipsychotic trials; 718 in antidepressant trials; 425 in trials of medication for social anxiety disorder; 136 for panic disorder; and 105 for obsessive-compulsive disorder.

According to Khan,

> [t]his was particularly surprising in light of the attempt, in most clinical trials, to exclude patients who are actively suicidal.
>
> In the case of trials for depression and anxiety disorders, suicide rates were in fact higher among those who received the investigational drug than placebo.

In July 2002, Irving Kirsch (University of Connecticut), Thomas J. Moore (The George Washington University School of Public Health and Health Services), and Alan Scoboria and Sarah S. Nicholls (also of the University of Connecticut) wrote an article titled: *The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration* wherein they report an analysis of the efficacy data submitted to the FDA for approval of six of the most widely prescribed antidepressants approved between 1987 and 1999. According to this analysis, 75 percent of the response to antidepressants is duplicated by placebo. Although approval of these medications implies that the data are strong enough and reliable enough to warrant approval, according to the authors, "[t]hese data were the basis on which the medications were approved by the FDA. If they are suspect, then perhaps the decision to approve the medications should be reconsidered."

The authors state in a later article that

> [t]he small difference between the drug response and the placebo response has been a "dirty little secret" [*Hollon, DeRubeis, Shelton & Weiss, 2002*), known to researchers who conduct clinical trials, *FDA reviewers*, and a small group of critics who analyzed the published data and reached conclusions similar to ours (e.g., *Greenberg & Fisher, 1989*). It was not known to the general public, depressed patients, or even their physicians. [Footnote omitted.] We are pleased that our effort facilitates dissemination of this information.

Antidepressants and Placebos: Kirsch, Moore et al., *Secrets, Revelations, and Unanswered Questions*, 5 PREVENTION & TREATMENT, Article 33, posted July 15, 2002.

Dan Troy is a former partner of the Washington law firm Wiley, Rein & Fielding, (a firm which has served the pharmaceutical industry for years). He is a former member of the industry-backed organization, American Enterprise Institute (AEI). AEI is an organization which lambasts the efforts of those who dare to litigate against not only the pharmaceutical industry, but big tobacco as well. In fact, Troy attacked the FDA's early attempts to regulate tobacco advertising. Troy, a former member of the American Advertising Federation ("a unifying voice of advertising") also made arguments before joining the FDA "that nearly torpedoed" limits on pharmaceutical company promotion of off-label uses of drugs. According to a recent *Washington Post* article "many public-interest attorneys think [Troy] is continuing the crusade he started" in his position as FDA Chief counsel.[5]

According to a December 22, 2002 *Boston Globe* article titled *FDA Counsel's Rise Embodies US Shift* by Michael Kranish, Troy's move from "relentless litigant against the FDA" to its "guiding legal star" illustrates how "a White House can use its administrative and legal powers to change the regulatory terrain without taking the often arduous course of asking Congress to change the law."

Having Troy as Chief Counsel for the FDA, according to Professor Richard Daynard at Northeastern University, "certainly does raise the question of the fox in charge of the chicken coop."

The *Boston Globe* article revealed, for the first time, that Pfizer's national counsel in the *Motus* case, Malcolm Wheeler (of the Denver firm, Wheeler, Trigg & Kennedy) "turned for help to one of the most powerful lawyers in the Bush administration: Daniel E. Troy, chief legal counsel of the United States Food and Drug Administration. Troy was quite familiar with the company, having served as a Pfizer attorney in legal combat with the FDA until just months before he joined the agency last year. Shortly after the one-year federal restriction on action involving his former clients expired, Troy filed a government brief that backed up Pfizer's case." Shortly indeed! Clearly, Troy is walking a very fine line.

Troy told Kranish that "as long as his mandated one-year recusal period was over on May 31—a year after he said he performed his last legal work for Pfizer—he didn't see any problem in filing a brief that helped" his former client. Troy reportedly argued: "When the recusal period was over, there was nothing wrong with getting involved."

Wheeler told Kranish: "I called Dan Troy and informed him of the case. This is a classic case in which the government's interests ought to be the same as those of a private company. Wheeler's spokesman said that Wheeler contacted Troy in July, but could not provide a date." (Wheeler has connections with GSK and its counsel as well. He filed an amicus brief in the Tenth Circuit on behalf of the "Product Liability Advisory Council, Inc." along with GSK's national counsel, Chilton Varner of King & Spalding (Atlanta, Georgia) after GSK was hit with an 8.4 million dollar jury verdict in a Paxil-induced murder/suicide case in Wyoming. The case was subsequently resolved and the appeal dismissed.)

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[5] *See* James V. Grimaldi, With Public Notice on First Amendment, FDA Appears on the Verge of Policy Shift, WASHINGTONPOST.COM, July 1, 2002.

When asked by Kranish, Troy declined to describe the work he did for Pfizer, or reveal how much he was paid. Plaintiff's counsel in the *Motus* case formally asked Dan Troy in early January 2003 to disclose what work he had conducted for Pfizer prior to his appointment as FDA Chief counsel and the amount of money he was paid for that work. To date, Mr. Troy has not responded. Plaintiff's counsel will raise this issue with the Ninth Circuit. Plaintiff's brief on the issue of federal preemption is due on March 10, 2003. Amicus briefs are due March 17th. Public Citizen will be filing an amicus brief.

As to the FDA's intervention in the Paxil class action, the *Boston Globe* article pointed out that

> Troy's office, which dispatches warning letters to drug companies about potentially false advertising, has cut the rate by which the FDA issues those warnings by two-thirds in the past year. Previously, such letters were sent out by a branch within the FDA. But Troy, after arriving at the FDA in August 2001, arranged for all warnings to go through his office.

Not only is the FDA's federal preemption arguments contrary to Congress' intent, it makes no sense in the context of its own stated circumstances. For instance, the FDA's Web site notes that "trends in a wide variety of external factors are generating workloads and public expectations that are poorly matched with FDA's capacity to respond in a timely, adequate manner." In an illustrative graph above this statement, titled "Growing Responsibilities Outpace FDA Resources," it is noted that Direct to Consumer Advertising is the largest growth trend "outpacing" the FDA's resources. Indeed, the FDA reportedly has only 14 employees to review 32,000 pieces of promotional material from drug makers.

The FDA, through its counsel, is grossly mischaracterizing the law in these cases. It argues that it is entitled to complete deference from the courts without being subject to judicial review. Our saving grace is that the FDA's authority is only as great as that granted by statutes and the Constitution. Unfortunately, for the plaintiffs involved in litigating these cases (wherein the FDA has intervened), it becomes a battle against not one formidable opponent, but another apparently even more formidable one whose interest is supposed to be to protect the consumer, not the pharmaceutical industry.

According to an article by James G. Dickenson titled *FDA's Law Chief is a Friend of Marketers*[6]: "The FDA Commissioner post has been vacant since George W. Bush took office" and until the post is filled, FDA's new Chief Counsel, Daniel E. Troy, is likely to "call the shots" within the FDA because "[t]raditionally, the FDA chief counsel's position has been one of immense, if subtle, influence over the agency."

Hopefully, now that the FDA has a confirmed Commissioner, he will rein in the agency's Chief Counsel.

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[6]James G. Dickenson, *FDA's Law Chief is a Friend of Marketers* 14 36(10) MEDICAL MARKETING & MEDIA (2001).