

STATE “FRAUD” SUITS OVER DRUG CLINICAL TRIAL RESULTS TREAD ON FREE SPEECH RIGHTS

by

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New York Attorney General Eliot Spitzer asserted a novel and potentially far-reaching fraud theory in his recent lawsuit against GlaxoSmithKline (“Glaxo”) for its dissemination of results of clinical trials of Paxil (paroxetine) on children and adolescents with Major Depressive Disorder. He claimed that Glaxo misled the public and the medical community by providing information concerning the drug’s clinical trials which yielded positive (or partially positive) results, but not those in which the results were negative or inconclusive. Shortly after the complaint was filed, Glaxo voluntarily posted full results of all clinical trials of Paxil on its website. On August 26, 2004, the case was settled on terms requiring a continuation of this practice, establishment of an online “Clinical Trial Register,” inclusion of safety and efficacy data in Medical Information Letters to physicians concerning off-label uses of drugs, and a payment of \$2.5 million. This settlement notwithstanding, Spitzer’s lawsuit raises significant issues about the First Amendment rights of drug manufacturers, the proper role of state attorneys general and other state regulators in a field already heavily regulated by the federal Food and Drug Administration (FDA), and the future utility of clinical testing. This LEGAL BACKGROUNDER analyzes the current state of preemption and First Amendment law and the reasons why cases of this nature, brought in the name of protecting the public, could end up producing quite a different outcome by creating incentives to cut short clinical drug trials that might be leading to negative or inconclusive results.

Background. Analysis of the Spitzer Complaint must begin with a brief overview of drug regulation in the United States. The FDA approves a drug for use by humans for treatment of specific diseases or conditions, based on a scientific assessment of the drug’s safety and effectiveness that includes extensive clinical testing. The particular uses for which the drug is approved are set out in the printed information which must accompany any dosages of the drugs dispensed by pharmacists. The contents of such notices, collectively referred to as the drug “label,” are subject to FDA regulation as well. That process is described in *Washington Legal Foundation v. Friedman*, (“WLF”), 13 F. Supp. 2d 51 (D.D.C. 1998), *vacated as moot on other grounds*, 202 F.3d 331 (D.C. Cir. 1999). Because the regulation of the practice of medicine (and most other professions) is traditionally the province of the states in our federal system, however, a licensed physician may prescribe a drug for uses other than those specified in the FDA-mandated disclosure. Such “off-label” uses are a well-established aspect of sound medical practice.

Mr. Spitzer’s Complaint noted that Paxil was approved by the FDA for treating various indications in adults, including MDD (Major Depressive Disorder), social anxiety disorder, general anxiety disorder and obsessive compulsive disorder (OCD). He described a series of clinical trials that Glaxo conducted of Paxil for the purpose of assessing its efficacy and safety in treating children and adolescents diagnosed with MDD. Allegedly, the results of the trials were mixed, with some indicating superior performance to a placebo and some a poorer performance. Some trials indicated a safety risk from side effects that included an increased risk of suicidal behavior, mood swings, crying and similar behavior.

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The heart of Mr. Spitzer' Complaint was the contention that Glaxo arranged for publication of a report that described only the results of a particular study that yielded the most favorable results. Acknowledging that some information regarding other trials was made available at a medical convention, he nevertheless asserted that neither these nor other allegedly negative trial results were ever published. Mr. Spitzer claimed that marketing efforts, including medical information letters, to physicians emphasized positive trials and made no reference to negative or inconclusive results. Yet the Complaint admitted that disclosures of the latter were made to regulatory agencies in the U.S., Canada and Europe. In fact, the disclosures to the FDA were made in an application for approval of the drugs for these currently off-label uses, in accordance with the Food and Drug Administration Modernization Act of 1997 ("FDAMA").

The Glaxo case has now been settled. In any future action of this type, however, certain issues are bound to figure prominently; two are the preemption doctrine and Glaxo's right under the First Amendment to engage in commercial speech.

Preemption. The Supreme Court's 1990 decision in *English v. General Electric Co.*, 496 U.S. 72 (1990) recognized three general circumstances in which state law is preempted under the Supremacy Clause: (1) express preemption, where Congress has explicitly defined the extent to which its enactments preempt state law; (2) field preemption, in which state law purports to regulate conduct in a field that Congress intended federal law to occupy exclusively; and (3) conflict preemption, when compliance with both state and federal mandates is impossible, or when state law poses an obstacle to the accomplishments of the objectives of Congress. But the Court has reminded us in *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) that, even when considering statutory language that purports to expressly preempt state law, courts must still identify the precise domain expressly preempted by that language.

The preemption analysis takes on additional sensitivity when the question arises in the context of a field traditionally occupied by the States, for then a court must heed the presumption that the historic powers of the States were not to be superseded by the Federal Act unless that was the clear intent of Congress. FDAMA contains specific provisions on the dissemination of information concerning the safety, effectiveness or benefit of an unapproved use of a previously approved drug, subject to certain conditions discussed in more detail below. For preemption purposes, the relevant provisions of the Act notably contain no outright prohibition on state regulatory activity, nor (unlike the Medical Device Amendments) do they contain any bar on states adopting differing standards. Accordingly, the express and conflict preemption doctrines will not apply. This leaves field preemption.

Attorney General Spitzer described his case as one "to stop [Glaxo's] illegal and deceptive actions." The dissemination of information about clinical trials of prescription medication plainly relates to the health and safety of the public, a field traditionally left to the states. That alone is not conclusive, however, for the preemption doctrine has been found to bar any number of state law causes of action, even when the context bears a direct relation to the public health. In the 2001 Supreme Court decision in *Buckman Co. v. Plaintiff's Legal Committee*, 531 U.S. 341 (2001), preemption barred a state law tort action regarding allegedly defective orthopedic bone screws, where the alleged fraud occurred in the manufacturer's submission to the FDA. The Court had little difficulty reaching this conclusion since the alleged fraud was against the FDA itself, and thus the very statements in question were occasioned by the Medical Device Amendments Act.

The prospects for a successful preemption argument are informed further by the D.C. Circuit's decision in *WLF*, a case involving FDA's Guidance Documents concerning distribution of "enduring materials" (journal articles and textbooks) and sponsorship of Continuing Medical Education (CME) programs regarding off-label uses of prescription drugs. The District Court held that the Guidances violated the First Amendment, but, during the pendency of the case, Congress passed FDAMA. The Act contains several provisions concerning manufacturer distribution of enduring materials that superseded those struck down by the District Court. Dissemination of enduring materials is permitted under the Act if several requirements are satisfied: application for approval for the off-label use, prior submission to FDA of the materials proposed for dissemination, a statement accompanying the distribution of the materials that they

relate to an unapproved use of the drug, and inclusion, if the FDA deems it appropriate, of “additional objective and scientifically sound information . . . necessary to provide objectivity and balance.” On appeal, the FDA confirmed to the D.C. Circuit that it viewed the Act’s requirements as creating a “safe harbor,” *i.e.*, compliance would shield a pharmaceutical company from misbranding or “intended use” enforcement actions. Notably, the FDA specifically disavowed any claim to independent prosecutorial authority under the Act. Likewise with respect to the CME Guidance, the FDA stipulated that if a drug manufacturer were to recommend content to a program provider that “runs afoul of all the Guidance’s twelve ‘factors’ that, by itself, is not a violation of law.”

Given the FDA’s representations to the D.C. Circuit in *WLF* regarding the nature and scope of its authority under FDAMA, a persuasive argument for preemption against Spitzer’s complaint is difficult to articulate. Even the Medical Device Amendments to the FDA Act, which contain an explicit provision barring the imposition of differing standards by the states, has been held not to preempt certain state law claims. Whatever FDA’s view of its authority under the Modernization Act, the state Attorneys General had a developed practice of bringing consumer protection actions during the years when the FDA operated under its predecessor statutory authority. It therefore seems unlikely that the case can be defeated on preemption grounds.

First Amendment. The Spitzer suit raises significant issues regarding the First Amendment protections for pharmaceutical companies’ dissemination of clinical trial results. It is highly unlikely, especially given the concessions made by the government in *WLF*, that a court would find such activity devoid of First Amendment protection simply because the FDA has extensive regulatory authority over the industry in general. The question is whether such communications should be considered primarily scientific, and thus “pure” speech or commercial speech. The former is entitled to maximum protection under the First Amendment, though commercial speech is also protected, albeit to a somewhat more limited degree. Distinguishing between the two entails consideration of three factors: (1) whether the speech is conceded to be an advertisement; (2) whether a specific product is identified and (3) whether the speaker has an economic motivation for engaging in the speech.

Application of these factors to dissemination of clinical trial results will probably yield the conclusion, as was the case in *WLF*, that such activity is properly classified as commercial speech. As such, the trial results nevertheless enjoy a strong measure of First Amendment protection, and the limits on that protection are well defined by the Supreme Court in *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557 (1980). The government may regulate commercial speech within certain limits: (1) if it is misleading or concerns illegal activity, the speech enjoys no protection; (2) if the speech is neither misleading nor related to illegal activity, the government must assert a substantial interest to be achieved by restrictions; (3) those restrictions must directly advance the state interest and will not pass muster if more limited restrictions could serve the government’s interest.

The First Amendment does not protect commercial speech about unlawful activity, but off-label uses of prescription drugs are not illegal when prescribed by a licensed physician. Clinical trial results of tests pertinent to off-label uses therefore do not relate to illegal activity. False or misleading commercial speech is not protected, but as the Supreme Court noted in *Ibanez v. Florida Dep’t of Business and Professional Regulation*, 512 U.S. 136 (1994), it is not enough to say that the speech is merely “potentially misleading.” The real question is whether the speech is inherently misleading, more likely to deceive the public than inform it. Applying these factors in *WLF*, the District Court concluded that peer-reviewed journal articles and CME materials were not inherently misleading.

The same conclusion should apply with respect to clinical trial results. The trials are conducted under tightly controlled scientific conditions, and the results are conveyed in terminology and analytical forms that practicing physicians are trained to understand and assess. No single trial purports to be the sum total of all accumulated knowledge on the question, nor is a physician likely to so perceive it. Those physicians, moreover, are free to seek and obtain information about the drug from other sources. The Spitzer

Complaint acknowledged that Glaxo had submitted Paxil for approval for treatment of children and adolescents, and included in that submission information regarding both positive and negative clinical trial results. The FDA subsequently issued two “Talk Papers” concerning Glaxo’s application, so it would appear that Glaxo complied with FDAMA’s requirements.

Under the second element of the *Central Hudson* test, the government plainly has a substantial interest in protecting the health and safety of citizens. But that level of generality will not advance the analysis in any meaningful way; “public health and safety” stands at the same level of all-consuming generality as “potentially misleading” does for the first prong of the *Central Hudson* test. In *WLF*, the Court squarely rejected an argument that the government could prohibit dissemination of materials on off-label uses out of fear that physicians would not be able to evaluate them properly, describing that purported justification as “practically an engraved invitation to have the restriction struck.” 13 F. Supp. 2d at 70 (citation omitted). But the Court found that the government did have a substantial interest in compelling manufacturers “to get off-label uses on-label.”

The Spitzer Complaint asked that the allegedly “deceptive, fraudulent and unlawful practices” of Glaxo be enjoined. Yet Glaxo appears to have complied with the FDAMA by submitting the clinical trial results to FDA, which in turn issued its own statements to the medical community. Under these circumstances, a future complaint seeking a ban on further dissemination would warrant the same fate accorded to the FDA’s request in *WLF*. And for the states, the goal of getting off-label uses on-label is not within reach, for that power lies with the FDA. A complaint like Mr. Spitzer’s, therefore, should be vulnerable on the second step of the *Central Hudson* test.

Even if a complaint somehow survived this step, the third element of the *Central Hudson* test would have to be considered. A request for broad injunctive relief and monetary damages or penalties may be seen as directly and materially — if bluntly — advancing whatever interest the state may have. But that request, read literally, should fail resoundingly for imposing burdens on substantially more speech than necessary. A request for an injunction against allegedly deceptive practices would entail: (1) a complete ban on the dissemination of clinical trial results; (2) some sort of government-managed dissemination, in which particular combinations of trial results, presumably good, bad and inconclusive, will have to be packaged together; or (3) a possibility raised by Judge Lamberth in *WLF*: full, complete, and unambiguous disclosure by the manufacturer. The first will fail as unduly restrictive, the second is not only unworkable but almost inevitably would entail content-based regulation of speech, and the last would involve government compulsion of speech, equally unacceptable.

Moreover, consider the practical impact of mandatory disclosure of all clinical trial results. A pharmaceutical manufacturer monitoring the progress of a given trial will be alert to the course of the research. As soon as the possibility of a negative or even inconclusive outcome emerges, the trial could be halted. No results will exist to be disseminated. But more importantly, research activity will be constrained, and medical science will know less about the potential benefits, as well as the possible dangers, of pharmaceutical products. It would be ironic indeed if a lawsuit brought in the name of the public health were to produce that outcome.

Conclusion. Attorney General Spitzer brought a case to regulate the dissemination of clinical drug trial results that advanced a bold and potentially troublesome theory of liability. Although future cases are not likely to be barred by the preemption doctrine, they carry a significant potential to intrude upon the First Amendment right of pharmaceutical manufacturers to engage in commercial speech. That commercial speech plays an important role in educating physicians on the possible uses of prescription drugs. Compulsory disclosure of all clinical trial results poses a real danger that pharmaceutical companies will simply cut short those tests that might be headed toward negative or inconclusive results, to the detriment of medical science in the short term and in the long run to the public health in general. The Spitzer Complaint and any others to follow are simply ill-conceived.