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Pandora's Box: Clinical Trial Data in Mass Tort Litigation Against Pharmaceutical Companies in the US

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"Big Pharma" - A Bull's Eye On Its Back

Pharmaceutical companies have become by far the most frequent target of mass tort litigation in the United States. This is attributable to three basic factors: (1) new statutes limiting other types of litigation, such as securities fraud and medical malpractice claims; (2) the relative failure of traditional mass tort cases against other targets such as the tobacco industry; and (3) the advent of direct-to-consumer advertising, which in some states has resulted in the dilution of the previously impenetrable defence of the learned intermediary doctrine, under which an adequate warning to a physician was deemed to satisfy the manufacturer's duty of care. Allied with these factors has been criticism of the drug approval process, and particularly the role played by the agency responsible for approving new drugs, the United States Food and Drug Administration ("FDA"). Allegations that the agency has failed the American public by approving drugs later found to have undisclosed side effects have shaken public confidence in the system, and have attracted the attention of plaintiffs' lawyers looking for the next deep pocket from which to claim multi-million (or billion) dollar verdicts.

Over the last five years, America has witnessed the filing of literally hundreds of thousands of individual lawsuits against pharmaceutical companies, not just by individuals who claim to have suffered personal injuries but also those who, while uninjured, now claim they would not have purchased the drug if they had known all the potential side effects. Third-party payors such as health insurance companies are joining the fray, seeking to recover the money they paid to reimburse consumers for drug purchases. These cases, frequently accompanied by claims for punitive damages, can threaten the very existence of a company, even if it acted properly in the development, marketing and approval of a drug.

Plaintiff Strategies For Victory: Some Old, Some New

To convince juries that manufacturers acted inappropriately, plaintiffs' lawyers employ some of the same tactics used in prior litigation against other industries. The clearest example is the "demonising" of the defendant. The phrase "Big Tobacco" has been replaced by the term "Big Pharma." Companies are accused of putting "profits before patients" or "sales before science," and treating people as "cash machines" where a prescription is nothing more than a contribution to the company's bottom line.

However, pharmaceutical cases also present a challenge not present elsewhere - the role of the federal government in approving the drug at issue. Since approval involves a determination that a drug is "safe" and "effective" for its intended use when accompanied by an adequate warning, which the FDA itself approves, plaintiffs must overcome the otherwise reasonable conclusion that an approved drug is safe and effective and that the warning labels on the drug are adequate. To accomplish this feat, plaintiffs' lawyers seek to persuade juries that the FDA wasn't given "the whole story," that certain facts, especially clinical trial data, were hidden from view, and that the manufacturer somehow hoodwinked the government into approving the product. This goes hand-in-hand with the theory that consumers weren't told the whole story either; that the warning - while approved by the FDA - was inadequate and that consumers should have been provided with additional information which, if disclosed, would have altered their decision to use the drug.

It is in this context that plaintiffs' lawyers focus on the clinical trial process leading up to the regulatory approval of a prescription drug.

Clinical Trials In The United States

Upon completion of pre-clinical research (in vitro and in vivo animal studies), a new drug manufacturer submits an Investigational New Drug ("IND") application to the FDA, seeking permission to initiate testing in human subjects. The IND application process consists of three phases of human studies or clinical trials. 21 C.F.R. § 312.21. These studies then form the basis of the manufacturer's New Drug Application ("NDA"). An NDA application requires the manufacturer to submit to the FDA "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(a).

Phase I

The purpose of Phase I trials is to examine the general safety of the new drug, identify potential side effects, and determine the appropriate dosing range for subsequent phases. 21 C.F.R. § 312.21(a). Phase I trials usually involve healthy volunteers, are shorter in duration and include fewer test subjects, ranging between 20 and 80. Id.

Phase II

Phase II trials include controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or

indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects. 21 C.F.R. § 312.21(b).

Phase III

Phase III studies are expanded controlled and uncontrolled trials. They are "intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling." 21 C.F.R. § 312.21(c). Phase III studies usually include from several hundred to several thousand subjects. Id. Phase III studies are double-blind and randomised, providing the cornerstone of the NDA. 21 C.F.R. § 314.126.

Phase IV

Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase IV) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but are not limited to, studying different doses or schedules of administration than were used in Phase II studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time. 21 C.F.R. § 312.85.

Limits of Clinical Trial Data

In a perfect world, manufacturers and regulatory agencies would be able to predict with certainty the long-term benefits and side effects of new drugs. However, the reality is that such information can be gained only from long-term studies, and society has made the judgment that the benefits of new drugs outweigh the risk that some unexpected side effect will manifest itself ten or twenty years down the road. The clinical trial process is intended to give the best information possible for the regulatory agency to make an educated decision about the likelihood that a drug's potential benefits outweigh its risks. However, clinical trials do not - indeed cannot - provide a guarantee that a drug will be safe and effective in the longer term.

Clinical trials also have other limitations. First, there are too few subjects in most clinical trials to uncover rare adverse events. Even the largest studies involve only a limited number of subjects and very rare side effects may emerge only after a medication is in widespread use among the general population. Second, because of stringent inclusion and exclusion criteria based on factors like age, gender, race, co-morbidities and concomitant use of medications, the test subjects are relatively homogenous. The actual user population is much more heterogeneous. Third, more relaxed laboratory and adverse event monitoring typical of general clinical practice may increase the chance that a minor side effect escalates to a more serious condition before the medication is discontinued and treatment initiated. Finally, to the extent that physicians prescribe a medication for off-label uses or at unapproved doses, clinical trial data will likely have limited use.

Plaintiffs' Use of Clinical Trial Data

Clinical trial data is an important weapon in the plaintiff lawyer's arsenal, and is used both to prove their claims and rebut the pharmaceutical manufacturer's defences. All of these theories are used to undermine the suggestion that the FDA or consumers were fully informed about the risks or side effects posed by the particular drug:

1. *Failure to disclose all relevant data*. Consistent with their "sales over science" theory, plaintiffs frequently allege that the manufacturer deceived the FDA as to the risks and benefits of a drug by cherry-picking clinical trial data and concealing negative results, thereby deceiving the FDA into approving the drug. See, e.g., Blain v. Smithkline Beecham Corp., 2007 WL 178564, at * 2 (E.D. Pa. Jan. 25, 2007) (Paxil); Clark v. Hoffman-LaRoche, Inc., 2006 WL 1374516, at *3 (N.J. Super. May 2, 2006) (Accutane); In re Baycol Prods. Litig., 218 F.R.D. 197, 202 (D. Minn. 2003) (Baycol). Such allegations are frequently accompanied by testimony from an "expert" who offers the opinion that the regulatory agency would never have approved the drug if all relevant facts had been known. See, e.g., In re Rezulin Prods. Liab. Litig., 309 F.Supp.2d 531, 548 (S.D.N.Y. 2004).

There is a question under U.S. law whether such evidence is even permissible or whether it is barred by the doctrine of federal preemption, under which state law tort theories of liability yield to a conflicting federal law. In the landmark case of Buckman Co. v. Plaintiffs' Legal Committee, 531 U.S. 341, 350 (2001), the United States Supreme Court held that "[s]tate-law fraud-on-the-FDA claims inevitably conflict with the FDA's responsibility to police fraud consistently with the Administration's judgment and objectives"). However, lower appeals courts are divided on whether the plaintiffs can still use evidence of such practices to meet the elements of more traditional claims such as failure to warn, or to defeat immunity statutes in some states for pharmaceutical products approved by the FDA. See, e.g., Desiano v. Warner-Lambert & Co., 467 F.3d 85 (2d Cir. 2006); Garcia v. Wyeth-Ayerst Labs., 385 F.3d 961 (6th Cir. 2004) (reaching opposite conclusions on whether Buckman bars such theories). The FDA, for its part, takes the position that its approval of a product warning preempts failure to warn claims entirely. 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). Again, the courts are divided on whether the FDA is correct in this position. See, e.g., Colacicco v. Apotex, Inc., 432 F.Supp.2d 514 (E.D. Pa. 2006); McNellis ex rel DeAngelis v. Pfizer, Inc., 2006 WL 2819046 (D.N.J. Sept. 29, 2006).

2. *Failure to conduct appropriate clinical trials*. Supported by an "expert" who, with the benefit of hindsight, nit-picks the clinical trials conducted; plaintiffs also allege that clinical trials were conducted with a view towards gaining regulatory approval, rather than uncovering any possible risks. Typical attacks include:

(a) that the clinical trial protocol was improperly designed - that the types of studies were inadequate (not randomised, controlled or double-blind, failed to account for different doses, drug interactions, etc.); that there was an insufficient number of participants to detect adverse events; or that there was an insufficient diversity in the subject population in terms of age, gender or race.

(b) that the clinical trial was inappropriately executed - failure to follow FDA-approved study protocols, prematurely terminating studies producing negative safety results, withdrawal of subjects with emerging adverse events before adverse event fully manifests itself, sloppy record-keeping.

(c) that the clinical trial results are biased by the conflicting interests of clinical research organisations. With a limited universe of clients, the contract research organisations that conduct clinical trials are to some extent dependent on pharmaceutical companies for their financial security. While there are federal regulations mandating particular disclosures to the FDA, see 21 C.F.R. § 54.4, plaintiffs nonetheless seek to undermine the independence of the

clinical trial process. In some cases, they have even sued the clinical research organisations involved. See, e.g., Staples v. Merck & Co., Inc., 270 F.Supp.2d 833 (N.D. Tex. 2003).

3. *Misrepresentation of Clinical Trial Results*. Plaintiffs also challenge the interpretation of clinical trial data by manufacturers, both in submissions to the FDA and in post-approval presentations to physicians about the benefits and risks of a particular drug. Claims that the benefits are overemphasised, and risks understated, are again used to buttress the argument that the manufacturer misled regulatory agencies and the public, and to argue against the application of the learned intermediary doctrine.

4. *Delay in Conducting Phase IV Trials*. In some cases, the FDA requires pharmaceutical manufacturers to conduct Phase IV trials after a new drug is approved. These "post-marketing studies" are meant to address any lingering questions about a drug's safety and potential side effects that might not have halted the approval but that were important enough to warrant clarification. In March of 2006, an FDA report suggested that as of September 30, 2005, almost two-thirds of the Phase IV studies pledged by companies were still pending. In such cases, the delay in completing the study provides additional ammunition for plaintiffs' lawyers, who argue that the Phase IV study would have released vital information earlier and resulted in either an improved warning or, in some cases, withdrawal of the drug from the market entirely.

New Statutes Addressing Disclosure of Clinical Trial Data

In June of 2004, the State of New York sued GlaxoSmithKline ("GSK") alleging that, starting in 1998, GSK withheld negative information concerning Paxil, a prescription drug used to treat depression. While Paxil was approved by the FDA for use with adults, it was sometimes used by physicians "off-label" to treat children. New York claimed that GSK "misrepresented data concerning Paxil's safety and efficacy when prescribed for depression in children and adolescents." Specifically, it claimed that GSK conducted at least five studies on the use of Paxil in children and adolescents, but published and disseminated only one of these studies. The lawsuit alleged that GSK suppressed the negative results of the other studies, which suggested a possible increased risk of suicidal ideation. Shortly after the lawsuit was filed, GSK posted on its website its clinical studies on the use of Paxil in children and adolescents. Settling the New York case, it also agreed to establish an online "Clinical Trials Register" that would contain summaries of results for all GSK-sponsored clinical studies of drugs conducted after December 27, 2000. Going forward, GSK agreed to post such results within ten months of their completion. See August 2004 Settlement Agreement (available at www.oag.state.ny.us/press/2004/aug/aug26a_04_attach1.pdf).

This lawsuit, and emerging concerns about the use of clinical trial data in the drug approval process, have prompted both the federal and individual state legislatures to introduce legislation designed to regulate more closely the disclosure of clinical trial results.

A. State Legislation

In Maine, one of the first states to enact legislation on the topic, a pharmaceutical company is prohibited from advertising prescription medications unless the company has provided to the state health department information about the clinical studies of such drugs. Me. Rev. Stat. Ann. tit. 22, c. 605, § 2700-A (2005). Specifically, the manufacturer is required to disclose on the "publicly accessible Internet website of the federal National Institutes of Health or its successor agency or another publicly accessible website the following information concerning any clinical trial that the manufacturer conducted or sponsored on or after October 15, 2002: (A) [t]he name of the entity that conducted or is conducting the clinical trial; (B) [a] summary of the purpose of the clinical trial; and (C) [t]he dates during which the trial has taken place; and (D) information concerning the results of the clinical trial, including potential or actual adverse effects of the drug." Id.

Two additional states, Illinois and Virginia, also passed laws aimed at making clinical trial results more transparent. Unlike Maine, these states do not require the manufacturers to publish clinical trial data, and instead, put the onus on the state. The statutes provide that the state health authorities will direct the public, through relevant state websites, to publicly available information about clinical trials. 20 Ill. Comp. Stat. § 2310-280 (2007); Va. Code Ann. § 2.2-212 (2007). A number of other states (California, Maryland, New Jersey, New York and Vermont), have proposed legislation requiring pharmaceutical companies to register and/or report on clinical trials. Most of these bills require registration of clinical trials with the state health department for disclosure in either a state database or on the federal website, www.ClinicalTrials.gov. Yet other states (like Hawaii) limit disclosure of clinical trial data to prescription medications used to treat serious or life-threatening diseases.

While these proposals have laudable goals, differing state requirements are likely to create confusion and difficulty, not only for those obligated to comply with such requirements, but for the physicians and patients for whom the information is intended. For example, companies could be forced to report research concerning a single clinical trial in different formats, in various online data banks. Multiple laws could also result in a company disclosing greater clinical research regarding a medication in one state versus another. Depending on the state, the extent of information a consumer or physician might find regarding a manufacturer's clinical trial could vary greatly. A preferable solution is a federal standard, which makes the disclosure requirements uniform in all fifty states.

B. Federal Legislation

Fortunately there is action on this issue at the federal level. In 2004 and again in 2005, both houses of Congress introduced the Fair Access to Clinical Trials ("FACT") Act, which would require sponsors of both publicly and privately-funded clinical trials to register the results of clinical trials in a central database. See S. 470, H.R. 3196, 109th Cong. (1st Sess. 2005); H.R. 3196, 109th Cong. (1st Sess. 2005); S. 2933, 108th Cong. (2d Sess. 2004); H.R. 5252, 108th Cong. (2d Sess. 2004). These bills failed to make it through Congress, but the proposed legislation has been introduced a third time this year in the Senate. See S. 467, 110th Cong. (1st Sess. 2007).

C. Industry Initiatives

In addition to these legislative efforts, pharmaceutical manufacturers have stepped forward to make additional information from clinical trials available to physicians and the public. For example, in September of 2004, the Pharmaceutical Researchers and Manufacturer Association (PhRMA) launched an

online database of clinical trial information (www.ClinicalStudyResults.org). PhRMA's express purpose in creating the web-based repository was "making clinical trial results for many marketed pharmaceuticals more transparent." In launching the database, the organisation avowed its commitment to the "timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing regardless of outcome." The information contained in the database is meant to serve as "a source of information for practicing physicians and patients alike." Some companies (including Eli Lilly, Roche, Bristol-Myers Squibb, and GSK) have launched their own websites for this express purpose. Other companies have opted to participate in established registries or databases.

Impact of Increased Disclosure Requirements

While to date there have been no cases examining Maine's disclosure statute, this and similar statutes may have ramifications for pharmaceutical companies in mass tort cases. In traditional failure to warn cases, plaintiffs bear the burden of proving all elements of negligence, including, significantly, the alleged breach of a duty to provide adequate warnings. Restatement (Third) of Torts § 6 (2005)(publication forthcoming). Clinical trial disclosure statutes might alter the parties' burden of proof at trial through application of the doctrine of negligence per se. Under this theory of liability, "[a]n actor is negligent if, without excuse, the actor violates a statute that is designed to protect against the type of accident the actor's conduct causes, and if the accident victim is within the class of persons the statute is designed to protect." Restatement (Third) of Torts § 14 (2005) (publication forthcoming).

As the U.S. Supreme Court has noted, "[t]he violation of federal statutes and regulations is commonly given negligence per se effect in state tort proceedings." Grable & Sons Metal Prods., Inc. v. Darue Engineering & Mfg., 545 U.S. 308, 318-19 (2005). It is possible (and in some jurisdictions likely) that these new state statutes will be given the same effect. While states have interpreted and applied negligence per se differently, there are essentially three variations of the doctrine. Under the traditional doctrine, which is followed by the majority of state jurisdictions, negligence per se obviates the plaintiff's burden of establishing duty of care and breach. See, e.g., Schlimmer v. Poverty Hunt Club, 597 S.E.2d 43, 46 (Va. 2004). In these states, plaintiffs may argue that a violation of the disclosure statute is per se negligent, and that the only remaining triable issues are causation and damages. Other states have ruled that statutory violations constitute a rebuttable presumption of negligence. See, e.g., Bacon v. Lascelles, 678 A.2d 902, 907 (Vt. 1996). Upon proof of statutory violation, the burden shifts to the defendant to show that it did not act negligently. Id. at 907. The remaining states hold that statutory violations are evidence of negligence. See, e.g., Hansen v. Friend, 824 P.2d 483, 486-87 (Wa. 1992). Regardless of which standard a particular state applies, any failure to comply with the disclosure statute could present a significant new traction point for plaintiffs in litigation.

Another unintended but inevitable consequence of databanks with clinical trial data is that it will be used by plaintiffs' lawyers in search of the next mass tort. Manufacturers can expect such data to be painstakingly pored over by plaintiffs' lawyers and their experts, looking for the smallest red flag.

Conclusion

As the issue of federal preemption makes its way through the appellate courts, clinical trial data will continue to be mined by plaintiffs' lawyers for evidence to support their theories that pharmaceutical companies misled the FDA, placed "sales over science" and marketed products with unknown health risks to an unsuspecting public. Increased disclosure requirements in the coming years may provide an ever more fertile ground for future mass torts.

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