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Passports, Products, and Potential Problems: Exploring the Litigation Challenges Faced by Pharmaceutical Companies Conducting Clinical Trials Abroad

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A New Focus of Plaintiffs' Failure to Warn Lawsuits

United States pharmaceutical companies and non-United States companies doing business in the United States have faced a growing number of product liability lawsuits in recent years. Though varied in their facts, these lawsuits are all bound by a common thread: plaintiffs' allegations that the pharmaceutical company "failed to warn" of the risks of its product. To prevail in these cases, plaintiffs must establish that: 1) the manufacturer knew or should have known about certain risks; 2) the manufacturer failed to warn consumers about these risks; and 3) such a warning would have prevented plaintiffs' injuries. Unlike many other areas of mass tort litigation, pharmaceutical product liability litigation in the United States is complicated by the federal government's regulatory role. The United States Food and Drug Administration ("FDA") is responsible for ensuring that before a prescription drug is marketed in the United States, it is proven safe and effective for its intended use and is accompanied by adequate warnings. Pharmaceutical companies provide the FDA with data from clinical trials to establish a drug's safety and efficacy and aid in the formulation of its warnings. When initiating litigation regarding these FDA approved drugs, plaintiffs must overcome the logical conclusion that an FDA approved drug is safe and effective and bears adequate warnings. To do this, plaintiffs employ many different methods to establish that the manufacturer withheld, hid, or somehow manipulated the information it provided to the FDA and the public, leaving the FDA, healthcare professionals, and the general public with an incomplete picture of the drug's safety profile.

One approach plaintiffs use to attack the adequacy of a product's warnings is to focus on the pharmaceutical manufacturer's advertising and marketing. Through this approach, plaintiffs seek to demonstrate that the aggressive way in which the drug was promoted diluted an otherwise adequate, FDA approved warning. Recent changes in United States law regulating prescription drug advertising have expanded the reach of this attack. The birth of direct-to-consumer marketing has, in many states, eroded the Learned Intermediary Doctrine, which once protected manufacturers from liability if they provided an adequate warning to the physician. Today, American consumers receive information about prescription drugs, not only from their physicians, but also through television commercials and magazine advertisements, giving plaintiffs new ammunition in their attacks on a company's warnings.

In addition to focusing on advertising and marketing to support their failure to warn claims, plaintiffs are looking with increasing frequency to the ways in which a manufacturer conducted its clinical trials. In this context, plaintiffs accuse manufacturers of putting revenues before research. They claim that manufacturers failed to warn consumers, either by rushing drugs to the market without the proper clinical testing, or by hiding, delaying, or somehow manipulating the results of its clinical testing. Clinical trials can be essential to plaintiffs' failure to warn cases, especially for new drugs that have only been on the market for a short period of time and, as a result, do not have extensive post-marketing data. As pharmaceutical companies conduct more and more clinical trials abroad, plaintiffs' attacks on these trials are certain to intensify.

Clinical Trials in the United States

In order to obtain approval from the FDA to market a new drug in the United States, a manufacturer must first conduct pre-clinical research, which includes laboratory and animal studies. Once a manufacturer has completed its pre-clinical research, it may then submit an Investigational New Drug ("IND") application to the FDA, seeking permission to begin research with human subjects. These human studies, or clinical trials, are divided into four phases, the results of which comprise the basis of a manufacturer's New Drug Application ("NDA"). As part of its NDA, a new drug manufacturer must submit "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).

Before submitting its NDA, a manufacturer must test a drug on thousands of subjects to produce reliable data regarding the drug's efficacy and safety profiles. Clinical trials are designed to provide reliable efficacy and safety results for a specific population. Elements of clinical trials that ensure the reliability of the results include: 1) randomisation and blinding procedures; 2) consistent inclusion and exclusion criteria; 3) frequent and consistent laboratory monitoring; and 4) standardised, mandatory adverse event reporting. For all clinical trials conducted in the United States, the FDA mandates that an Institutional Review Board ("IRB") be created to monitor the trial and ensure the safety of clinical trial participants and the quality of the data. Unlike clinical trials, other forms of safety-related data, including meta analyses, epidemiological studies, and post-marketing adverse event reporting rates, are limited in reliability and susceptible to various confounders and biases that curtail their usefulness. Clinical trials, when properly designed and executed, are considered the gold standard for safety and efficacy data.

Phase I

In a Phase I trial, the new drug manufacturer studies the general safety of the drug, including the existence of any adverse effects and drug interactions, and determines the appropriate dosing range

for subsequent phases. These pre-marketing trials are generally made up of a small number of healthy volunteers, usually between 20 and 80, and are short in duration.

Phase II

In a Phase II trial, the new drug manufacturer studies the effectiveness of a drug for a specific indication. These pre-marketing trials are generally comprised of human subjects with the target disease or condition and are of intermediate size and duration.

Phase III

If Phase II trials indicate efficacy, the new drug manufacturer will conduct Phase III trials. In a Phase III trial, the new drug manufacturer studies in detail the safety and efficacy of its drug. These pre-marketing trials are large in size, usually several hundred to several thousand participants, and long in duration. Like Phase II trials, Phase III trials are comprised of subjects with the targeted disease or condition. Phase III trials are one of the most important parts of the NDA and are used to evaluate the risk-benefit profile of a drug, as well as to provide a basis for creating appropriate drug labeling information.

Phase IV

In a Phase IV trial, the new drug manufacturer studies various clinical outcomes. These post-marketing studies are large in size and long in duration and are often required by the FDA as a condition to NDA approval.

Rise of Foreign Clinical Trials

In recent years, the number of clinical trials conducted outside of the United States by American pharmaceutical companies seeking FDA approval of new drugs, has grown exponentially. This shift to "foreign clinical trials" is widespread outside of the United States as well, and represents a global trend. While the majority of these trials have taken place in countries with experience conducting clinical research, such as the United Kingdom, Germany, and Canada, these trials have recently expanded to countries far less familiar with the process, including Latin American, Eastern European, East Asian, and African countries. These "new" countries are considered desirable locations for clinical trials for several reasons. First, these countries have large populations of available "naïve subjects," that is, subjects who have not received any prior treatment for the targeted disease or condition. This can be particularly desirable to pharmaceutical companies, as it can be difficult to find subjects in the companies' home country who have not undergone some form of treatment for the targeted disease or condition. Pharmaceutical companies may also be interested in foreign naïve subjects, as they allow the companies to test the effects of their drugs on a particular racial or ethnic sub-populations, something that can be difficult, if not impossible, to achieve in their home countries. In addition to the desirability of the potential subjects, many of these "new" countries are also attracting clinical trials due to a lack of local regulatory barriers that can frustrate and slow the clinical trial process. Reduced regulations permit companies to enroll participants more easily, complete clinical trials expediently, and get their drugs to the market more quickly. In addition, these "new" countries provide untapped consumer markets for the sale of the experimental drugs once the clinical trial process is complete.

Yet, despite their benefits, foreign clinical trials pose potential problems for pharmaceutical manufacturers, particularly should the drug end up in litigation. A lack of FDA regulation and lenient international guidelines make foreign clinical trials prime targets for attack by plaintiffs in product liability litigation, which has the potential to create far-reaching problems for these manufacturers. Conducting such trials in newly developed nations also presents ethical concerns that deserve serious consideration.

Regulation of Foreign Clinical Trials

International Guidelines

Global human clinical trials are subject to four major international regulations. The Helsinki Declaration, first established by the World Medical Association in 1964 and most recently amended in 2000, is the oldest and most influential regulation. See Declaration of Helsinki, W.M.A. 52nd Assembly (Oct. 2000). The Helsinki Declaration sets forth the ethical standards for human clinical trials, emphasising that the well-being of human subjects should prevail over the interests of science and society. The other regulations, which incorporate many of the same principles articulated in the Declaration of Helsinki, are: 1) the International Ethical Guidelines for Biomedical Research Involving Human Subjects, which was adopted by the Council for International Organizations of Medical Sciences in 1993 and amended in 2002; 2) the Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products, adopted by the World Health Organization in 1995; and 3) the Guidelines for Good Clinical Practice, adopted by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use in 1996.

Though varied in some aspects of their protections, these regulations all share a heavy reliance on local researchers and ethics monitoring boards to provide informed consent and protect local human subjects. These international guidelines have been criticised for not doing enough to mandate the disclosure of potential conflicts of interest, for being influenced by the pharmaceutical industry, and for not providing enough protection to foreign study participants. Compounding the critique of these international guidelines is the fact that in an effort to appeal to pharmaceutical companies, and promote the technology and revenue that clinical trials might generate, many host countries do not regulate clinical trials.

Industry Guidelines

In 2002, the Pharmaceutical Research and Manufacturers of America ("PhRMA") promulgated "Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results." These principles were created by PhRMA to address: 1) the protection of research participants; 2) the proper conduct of clinical trials; 3) objectivity in research, and 4) the disclosure of clinical trial results. Due in large part to the fact that compliance with these principles is voluntary, these principles, like the international guidelines, have been criticised as not doing enough to protect foreign clinical trial subjects and to regulate the foreign clinical trial process. While acknowledging their voluntary nature, PhRMA stated that it believed these principles were effective and would be enforced by public opinion.

United States FDA Regulations

Foreign clinical trials can be a valuable source of information in the

FDA's determination of the safety and efficacy of new drugs. Currently the FDA accepts data from foreign clinical trials conducted in one of two ways: 1) under an IND; or 2) under either the Declaration of Helsinki or the laws of the host country, whichever provides greater protection to the human subject participants. See 21 CFR § 312.120. If a sponsor chooses to conduct foreign clinical trials under an IND, it must conduct its research according to FDA guidelines, which includes obtaining a signed attestation from each clinical investigator that he or she will conduct research in an ethical manner and in accordance with FDA regulations. The attestation includes commitments to inform subjects that the drugs are being used for investigational purposes, to report adverse events, and to report to the IRB any changes in the study protocol or any unexpected problems. See FDA Form 1572. A sponsor that opts not to conduct foreign clinical trials under an IND, must conduct those trials in accordance with the ethical principles of the Declaration of Helsinki or the host country's own regulations, whichever affords human participants the greater protections. Notably, clinical trials not conducted under an IND are not required to obtain attestations from the clinical investigators. Additionally, while it conducts domestic on-site inspections of IRBs, the FDA does not inspect foreign IRBs.

In recent years, many have called on the FDA to take a greater role in regulating foreign clinical trials and to require that all clinical trials submitted to the FDA, no matter where they were conducted, comply with U.S. standards, which offer more protection to study participants than any of the international or industry guidelines. The United States Department of Health and Human Services ("DHHS") recently authored a lengthy report, detailing the need for increased oversight of foreign clinical trials. See Janet Rehnquist, Office of the Inspector General, U.S. Department of Health and Human Services, The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects (Sept. 2001).

One of the measures DHHS recommended is that sponsors obtain attestations from non-U.S. investigators that they will adhere to ethical principles of research when conducting their clinical trials. DHHS further suggested that sponsors more vigorously monitor their foreign trials. On April 28, 2008, the FDA promulgated new regulations for foreign clinical trials not conducted under an IND, which will come into effect later this year. In an effort to increase protections for human subjects and provide greater assurance of the quality of the data obtained from foreign clinical trials, the FDA will delete the reference in its current regulations to the Declaration of Helsinki and replace it with a requirement that clinical trials not conducted under an IND be conducted in accordance with "Good Clinical Practices," which includes review and approval by an Independent Ethics Committee. This change is no doubt a step in providing greater protection to foreign clinical trial participants and an indication that greater international regulations may follow. However, at present the international regulatory environment concerning foreign clinical trials has not yet matured, putting more pressure on individual pharmaceutical companies conducting these trials to act in ways that will protect themselves, as well as their trial participants.

Challenges of Foreign Clinical Trials

Several years ago, Pfizer was sued in the United States under the Alien Tort Claims Act by Nigerian minors and their guardians who claimed that Pfizer had failed to abide by international standards for the protection of human clinical trial participants. See Abdullahi v. Pfizer, Inc., 2005 WL 1870811 (S.D.N.Y. Aug. 9, 2005). The case involved Pfizer's testing of Trovan, an experimental antibiotic used to treat meningitis. Plaintiffs claimed, in part, that Pfizer failed to keep proper records of the clinical trial, failed to obtain proper informed consent from the study participants, failed to conduct follow up examinations, worked in concert with the Nigerian government to hide inconsistencies in the data, and engaged in several other unethical practices. Although the case was ultimately dismissed for plaintiffs' failure to state a claim under the Alien Tort Claims Act, plaintiffs' allegations highlight some of the challenges pharmaceutical companies face when conducting foreign clinical trials and the arguments claimants' counsel can cobble together based on such trials.

Bias, Conflicts of Interest, and Overall Impropriety

Not surprisingly, one of the strongest critiques of foreign clinical trials is that the dynamics of the relationship between the host country and the pharmaceutical company incentivise improper conduct and, as a result, both parties fail to protect the interests of the local human study participants. One of the reasons American pharmaceutical companies find it easier to conduct clinical trials abroad is due to the support and cooperation of the foreign host countries. The enthusiasm of the foreign host countries often stands in stark contrast to the hurdles American pharmaceutical companies face when conducting these trials in the United States. Of course, the desire of the host countries to be home to clinical trials should not come as a surprise, as doing so comes with many benefits, ranging from free prescription drugs to new hospitals, clinics, and other medical facilities. The benefits can even include doubling or tripling the annual incomes of healthcare providers in the host country through salaries and recruitment fees.

Plaintiffs seeking to build a failure to warn case can easily attack this relationship. They claim that having received financial compensation, the host country administrators have an incentive to serve the needs of the pharmaceutical company, rather than the local study participants. In short, the studies are biased from the very outset. Furthermore, the desire to entice pharmaceutical companies to return to conduct additional trials may give host governments additional incentives to encourage local safety monitoring committees to deviate from research protocols by failing to report adverse events or allowing patients with adverse events to withdraw early, failing to obtain adequate informed consent from participants, or bending the inclusion and exclusion criteria of the clinical trial.

When embarking on foreign clinical trials in developing countries with less resources and clinical trial experience, pharmaceutical companies must be cognizant of the inherent inequities and incentives in the relationship. Companies must anticipate potential future attacks by potential claimants and take affirmative actions to increase the transparency of the clinical trial process, including keeping proper documentation of protocols, study data, informed consent, and all other pertinent communications. Companies must insure that they are providing study participants with adequate informed consent, one of the basic tenets of all of the international guidelines, and avoid the most obvious problems that can negate the adequacy of this consent, such as language barriers. Additionally, many companies have begun to create their own standards for clinical trials.

Foreign Corrupt Practices Act

In addition to planning for potential future products liability litigation arising out of the nature of the relationship between the pharmaceutical company and host countries, pharmaceutical companies must tread lightly with the "benefits" they provide to host countries in exchange for their work on clinical trials. While

there is a general rule in the International Conference on Harmonization guidance on Good Clinical Practices that all financial arrangements in a trial must be disclosed to the Ethics Committee, there is little other guidance on what benefits to a host country (equipment, training, infrastructure improvements) are permissible. Pharmaceutical companies must be extremely careful when providing these benefits not to run afoul of the Foreign Corrupt Practices Act, which prohibits bribery of foreign officials (including physicians in foreign government-owned hospitals) by United States company officials, either directly or through their agents. See 15 U.S.C. §§ 78dd-1 (1977). Violations of the Foreign Corrupt Practices Act can result in serious consequences, including multi-million dollar fines and even imprisonment of company officials. When conducting foreign clinical trials, pharmaceutical companies should watch out for certain red flags that could lead to a violation of the Foreign Corrupt Practices Act, such as consulting or contracting agreements that are not accompanied by a written contract or other businesses dealings that do not involve appropriate documentation. The threat of a violation of the Foreign Corrupt Practices Act is just another reason pharmaceutical companies conducting foreign clinical trials must take extra care to keep meticulous and thorough documentation of all aspects of the clinical trial process.

Study Design

In addition to arguing that the pharmaceutical company and the host country had an improper relationship, another way plaintiffs attack foreign clinical trials is by focusing on the clinical trial's design. Foreign clinical trial participants, sometimes called "naïve subject," are often coveted for their lack of prior treatment for the targeted disease and lack of co-morbidities, including smoking and obesity. Yet, when clinical trials are conducted in patient populations that differ significantly from the ultimate target populations to which the experimental drug will be marketed, companies open themselves up to a possible attack. Plaintiffs will contend that by studying the drug in human subjects without the same co-morbidities, concurrent medications, or racial makeup as the likely consumer, the new drug manufacturer did not test the safety and efficacy of the drug in "real world settings" and therefore failed to discover and ultimately to warn the consumer of certain risks. This argument applies to dosing as well, if there is a disconnection between the dosing studied in clinical trials and that recommended in the label.

Another aspect of the attack on a study's design is the "cutting corners" argument. One of the reasons pharmaceutical companies are conducting more and more clinical trials abroad is because it can be less expensive than conducting such trials in the United States. While there is nothing inherently untoward about seeking to conserve resources, plaintiffs latch onto this fact and argue that the company was cutting corners with patients' safety. Arguments regarding the design of clinical trials can be particularly useful to plaintiffs seeking to make a claim for punitive damages.

Ethical Considerations

Finally, though perhaps less apt to be used by plaintiffs in product liability cases, manufacturers must grapple with the ethical problems of conducting clinical trials of experimental drugs in developing countries and, once proven safe, ultimately selling those drugs only in wealthy countries. Many argue that distributive justice requires that American pharmaceutical companies leave the host countries better off than they found them. As discussed above, however, companies must be careful that the benefits provided to the host countries are not perceived as bribes and do not create conflicts of interest that can put the welfare of human subjects at stake. Striking the proper balance requires thoughtful consideration and planning on the part of the pharmaceutical company.

Conclusion

Clinical trials are the centerpiece of the new drug approval process in the United States. In recent years, they have also become the centerpiece of plaintiffs' failure to warn cases against pharmaceutical manufacturers. Drug manufacturers encounter further challenges when conducting these clinical trials in countries outside of the United States. As international guidelines and FDA regulations are still developing in this area, it is incumbent upon the pharmaceutical manufacturer to be proactive in working with the host country to develop appropriate trial protocols and to conduct well monitored clinical trials that will produce quality data. By taking affirmative steps to increase the transparency in the foreign clinical trial process, pharmaceutical companies will protect themselves, as well as their human clinical trial participants.

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