Clinical Trials: Strategies for Sponsor Manufacturers to Minimize the Risk of Litigation

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A recent Kansas federal court case confirms what sponsor manufacturers of clinical investigations of new drugs and medical devices have argued for years: Sponsor manufacturers discharge their duty to warn of potential risks of the drug or medical device by providing adequate warnings to the investigator, who acts as the "learned intermediary." This is true regardless of how the investigator chooses to administer informed consent, as liability for any flaws in the process lies with the investigator. Similarly, the sponsor manufacturer has no duty to (1) determine whether the benefit to the patient outweighs any risks from ingesting the drug; (2) secure the patient's informed consent; or (3) supervise the patient during the study. All these responsibilities lie with the investigator. More important, recent case law confirms that a sponsor manufacturer can take affirmative steps to avoid or reduce potential liability in connection with clinical studies. This article continues a discussion, begun in the December 2001 issue of the Pharmaceutical and Medical Device Law Bulletin, Law Journal Newsletters, Vol. 1, No. 12, of litigation in the context of clinical studies ("Part I").

In *Kernke v. The Menninger Clinic Inc.*, 173 F. Supp. 2d 117 (D. Kan. 2001), plaintiffs brought claims against Aventis Pharmaceuticals Inc. for, inter alia, failure to warn, negligence and breach of warranty in connection with the investigation of a new drug, M100907, for the treatment of schizophrenia and schizoaffective disorders. Aventis' predecessor, Hoechst Marion Roussel Inc., was the maker of the drug. The clinical study at issue was designed to test the safety and efficiency of M100907 in comparison to a placebo and another drug, haloperidol. The decedent, an inpatient at Menninger Clinic and a diagnosed schizophrenic, executed informed consent documents for each part of a two-phase study. During phase two of the study, however, the patient wandered off from a clinic-supervised outing unrelated to the study and was found dead some months later in a wooded area on the clinic's grounds. Exposure was listed as the probable cause of death.

The court held that Aventis had discharged its duty to warn by providing appropriate warnings about the drug to the learned intermediary-the investigators. First, Aventis had complied with its obligations under applicable federal regulations prior to the commencement of the study by (1) submitting study protocols to the FDA for review; (2) obtaining approval to proceed from the FDA before commencing the study; and (3) providing the investigators (including the clinic) with a written investigational drug brochure (IDB), which included all the known adverse events reported by prior study participants, as well as updated safety reports. Second, Aventis obtained the investigators' agreement that they, inter alia, (1) would administer informed consent to all study participants; (2) had read and understood the IDB; and (3) would exercise their independent medical judgment to determine whether a prospective study participant was compatible with the study protocol. 173 F. Supp. at 1119-20. See also *21 CFR Section 312.53*.

As Kernke recognized, under applicable federal regulations, sponsor manufacturers may delegate investigative duties to other persons and entities. *21 CFR Section 312.50 et seq.* Courts agree that once the duties are delegated to an investigator, liability for any failure to properly execute them lies with the investigator.[1] Indeed, the court explicitly rejected an attempt by plaintiff to carve out an exception to the learned intermediary rule if there were irregularities in the administration of informed consent by the investigator, finding no duty on the part of the sponsor manufacturer to monitor the investigator. Accordingly, no failure to warn claim could be sustained by plaintiffs against the sponsor manufacturer. In connection with plaintiff's negligence claims, the *Kernke*

court held that the sponsor manufacturer had no duty to study participants to (1) determine whether the participant was an appropriate candidate under the protocol; (2) obtain his or her informed consent; or (3) supervise him or her during the study. Again, investigators bear this responsibility. Therefore, each of these claims was dismissed.

Strategies for Manufacturers to Minimize Exposure

Kernke reminds us that sponsor manufacturers can take a number of precautions to minimize or prevent liability arising from the investigation of new drugs and medical devices. These strategies fall into at least three key categories: (1) compliance with applicable federal regulations; (2) creation of a clearly delineated relationship with the investigator through preparation and execution of a thorough clinical research agreement; and (3) maintenance of the patency of the learned intermediary defense by avoiding actions that remove the investigator from that role.

Compliance with applicable federal regulations should include, but is by no means limited to, those actions the *Kernke* court found to be critical:

- Submitting a study protocol to the FDA for its review.
- Obtaining FDA approval before proceeding with the study.
- Advising the investigator of all known adverse events and safety reports through a written brochure.
- Obtaining a signed investigator statement/agreement. See *21 CFR Sections 312.40* and *312.50 et seq.* for specific requirements.

Preparing and executing a written agreement with the investigator can be a lengthy process, although pharmaceutical companies generally rely on well-vetted form agreements. Special attention should be paid to setting forth detailed arrangements for the study, including delineation of the investigator's obligations. Moreover, the agreement should include an indemnity clause, such as the following:

> Sponsor shall indemnify and hold harmless Institution and Principal Investigator ("Indemnitees") from and against losses, damages, claims, suits and reasonable costs and expenses, including the reasonable cost and expense of handling and defending such claims and suits, that are directly attributable to Institution's testing of the Compound pursuant to the Study; provided that Indemnitees have complied with (i) all the terms of this Agreement and the Study; (ii) all dosage and other specifications, directions and recommendations furnished in writing by Sponsor for the use and administration of the Compound; and (iii) all FDA and other applicable laws, rules and regulations.[2]

More recently, manufacturers have also sought to include a reverse indemnification provision requiring indemnification of the sponsor by the investigator. Although neither provision provides immunity from litigation, both have the potential to reduce a sponsor manufacturer's exposure.

Finally, allegations of an agency relationship between sponsor and investigator have the potential to derail a sponsor manufacturer's learned intermediary defense to failure to warn claims. Although it may help to state clearly in the written agreement that the investigator is not an agent of the sponsor, avoiding the appearance of agency is most critical. In *Tracy v. Merrell Dow Pharmaceuticals Inc.*, 58 Ohio St. 3d 147, 569 N.E.2d 875 (1991), plaintiff argued that the physician was a mere agent of the manufacturer, and not a learned intermediary, because the manufacturer had paid the physician investigator $15 for each patient enrolled in the study. The Ohio Supreme Court rejected the argument because it found that under the facts of that case, the fact that the manufacturer paid financial incentives did not prove that the physician set aside his or her independent medical judgment in communications with the patient. Thus, the analysis of the existence of an agency relationship will focus on whether the monetary incentive caused the investigator to set aside his or her independent medical judgment in, for example, determining whether a patient was an appropriate candidate for the study under the protocol.

Nevertheless, manufacturers sponsoring clinical studies should avoid offering financial incentives to the investigators to enroll patients. At a minimum, the sponsor must ensure that the investigator discloses any such incentives to the patients, and agrees that notwithstanding the incentive, the investigator will exercise independent medical judgment in selecting candidates for the study.

Moreover, sponsor manufacturers must be aware that whenever possible, plaintiffs will argue that the learned intermediary defense does not apply because, for example, the investigational drug or device was marketed or distributed directly to the patient. See, e.g., complaint in *Abdullahi v. Pfizer Inc.*, No. 01 CV 8118 (S.D.N.Y. filed Aug. 28, 2001) (alleging that Pfizer representatives traveled to Nigeria and directly distributed the investigational drug without obtaining informed consent). Companies therefore must avoid directly marketing or distributing investigational drugs to patients, or otherwise removing the physician as a learned intermediary, as this practice may defeat a critical, and otherwise valid, defense.

Responding to New or Imminent Litigation

Plaintiffs typically assert traditional product liability claims even in the context of litigation arising out of their participation in clinical studies. Accordingly, the defense strategies for litigation arising out of clinical studies are familiar ones.

First, the sponsor manufacturer should assemble a team of individuals knowledgeable about the clinical study and investigate, inter alia, the following facts:

- What was the scope of the investigator's responsibilities?
- Was the protocol followed?
- What were the circumstances under which informed consent was obtained?
- Was written consent obtained?
- Was an approved consent form used?
- Did the investigator depart from its obligations under the research agreement?

Second, the sponsor manufacturer should retain outside counsel and evaluate the complaint with regard to the spectrum of available defenses:

- How strong is the learned intermediary defense?
- Do plaintiffs have an agency argument?
- For Section 1983 claims, is there "state action" such as government involvement in the study?
- Are plaintiff's Nuremberg Code and/or "international law" claims linked to a self-executing law?[3]
- Does preemption apply?

Next, the sponsor manufacturer should assess liability and determine whether other parties should be impleaded. Moreover, during the course of the litigation, the sponsor manufacturer should seek dismissal of plaintiff's claims aggressively, especially "lack of informed consent" claims, which lie only against the investigator.

In addition, the sponsor manufacturer should assess the strength of a challenge on medical causation grounds by:

- Determining what adverse events are claimed;
- Thoroughly investigating the patient's medical history; and
- Retaining experts to evaluate the science.

Thereafter, the sponsor manufacturer can evaluate the likely success of a motion for summary judgment based on lack of medical and/or alternative causation, or other grounds.

Lessons from Kernke

The summary judgment achieved by Aventis in *Kernke* is an excellent example of the outcome a sponsor manufacturer can expect from a prompt investigation of the facts and the assertion of key affirmative defenses. Of those defenses to plaintiff's failure to warn claims asserted by Aventis, the learned intermediary defense remains the most critical one to assert around the country. Indeed, the learned intermediary defense also forms the basis of courts' and states' continued refusal to permit lack of informed consent claims against sponsor manufacturers to proceed to a jury, because the administration of informed consent lies within the province of the investigator physician. See *Gaston v. Hunter*, 121 Ariz. 33, 588 P.2d 326 (Ct. App. 1978) (for a more detailed discussion of this type of claim, see Part I of this series).

In sum, with careful risk management, a sponsor manufacturer can reduce the frequency of claims arising out of clinical studies. If litigation does arise, a sponsor manufacturer can defeat such claims by using many of the same strategies employed to defeat litigation in the post-market approval stage.

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[1]For example, a contract research organization retained to conduct a study takes on all obligations prescribed by the regulations for sponsors, including oversight of the study. *21 CFR Section 312.52(b)*.

[2]This excerpt of an indemnification provision is offered as an example only. Its inclusion is not intended as legal advice or a representation as to whether the provision as worded is enforceable in a court of law.

[3]See Part I of this series for a discussion of claims based on Section 1983 and the Nuremburg Code.