Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies

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This paper outlines several major issues relating to legal liability for exclusion or inclusion of women as subjects in clinical studies, excluding liability exposure for injury to offspring. The principal focus of the paper is on the testing of pharmaceutical products, because the page constraints make it impossible to cover in depth the issues relating to all types of clinical studies.

The term "clinical studies" encompasses a wide range of activities. In pharmaceutical testing, it usually refers to randomized clinical trials, using either a placebo or an established therapeutic as the control. Clinical studies also include the early-phase safety studies in healthy volunteers, postmarketing studies to expand the indications for use or to investigate safety and effectiveness in special populations (e.g., elderly or children), and investigations of the outcome of health interventions.

Various actors are involved in clinical studies. Companies sponsor studies of pharmaceutical or medical device products; physician investigators conduct and monitor studies; institutional review boards (IRBs) review and approve proposed protocols and informed consent; research institutions provide the study site and may provide attendant medical care; and the Food and Drug Administration (FDA) administers federal statutes and regulations that govern the conduct of clinical investigations, the data required to support product approval applications, and the information contained in product labeling. At least in theory, each of these actors is subject to potential liability for an injury incurred in connection with a clinical study. \(^1\)
It is important to bear in mind that the law is dynamic, not static. New scientific information and new legal theories can quickly change the liability landscape.

One significant change is the way that clinical studies are viewed. Prior to 1981, the focus was on abusive practices in medical research, especially involving women and the elderly, and the need for enhanced protection of human subjects.²

Now, some commentators assert that participation in clinical trials should be considered a right, especially where the studies involve potentially lifesaving therapies or important research on health outcomes. In considering these different views, recall that some "clinical studies" may involve potentially significant benefits to the participant, while others may involve only sacrifice (e.g., in healthy volunteers) or the element of chance inherent in randomization to a study group. Thus, while inclusion of women in clinical studies may be good for women as a whole, it may or may not be beneficial for the particular women included in a particular study.

**TORT LIABILITY DOCTRINES**

The actors involved in clinical studies are subject to potential liability in various forms, including product liability lawsuits, medical malpractice actions, or professional licensing board investigations. Even if you are likely to prevail in an action brought against you, the fear of becoming involved in such a legal proceeding is a very strong factor affecting decisions concerning clinical trials. A lawsuit or investigation entails substantial burdens and costs, including the disruption of ongoing work, psychological effects on the individuals who have been accused of causing or contributing to an injury, attorney fees, litigation costs, adverse publicity, and perhaps the costs of settling the plaintiff's claims. Thus, individuals are highly motivated to take the course of action -- such as excluding women from clinical trial -- that appears most likely to eliminate or greatly reduce the risk of becoming involved in a legal proceeding.

The most significant basis of legal liability for exclusion or inclusion of women as subjects in clinical studies is tort liability.³ When a plaintiff alleges tortious injury from a drug product, two legal theories are likely to be asserted: negligence and strict liability. In a negligence action, the plaintiff must prove that (1) the defendant (e.g., the manufacturer or investigator) had a legal duty toward the plaintiff, (2) the defendant breached that duty, (3) the plaintiff suffered an injury, and (4) the defendant's breach of its duty was the cause of the plaintiff's injury.⁴ In a drug product liability case, the plaintiff would show, for example, that he or she was not given the information that should have been given and that this lack of informed consent caused the plaintiff's injury.
Under strict liability, the manufacturer of a product that is "in a defective condition unreasonably dangerous to the . . . consumer" is subject to liability for injury caused to the consumer without proof of fault by the manufacturer. However, "unavoidably unsafe" products are exempted from this general rule, provided the manufacturer has properly prepared them and has given proper direction and warnings for the products. This exemption (known as the comment k exemption under the Restatement (Second) of Torts § 402A) has been applied by a majority of state courts to prescription drugs and vaccines. Thus, a prescription drug will not be considered unreasonably dangerous if it is accompanied by adequate warnings of potential side effects. Although section 402A expressly applies to sellers of goods, it potentially applies even to those manufacturers who provide investigational drugs free of charge.

Under the so-called learned intermediary doctrine, manufacturers generally can satisfy their duty to warn regarding both prescription drugs and investigational drugs by warning the medical community rather than the ultimate consumer. Warnings are provided through informed consent and the investigator's brochure for investigational products, and through product labeling for marketed products.

The applicability of comment k to prescription drugs varies from state to state. California and Utah have expressly ruled that comment k applies to all properly prepared drugs accompanied by adequate warnings. Wisconsin and Alaska, on the other hand, have refused to adopt comment k and thus declined to protect drug manufacturers from strict liability. The rule in many states is that prescription drugs, prescription medical devices, and vaccines should be accorded the comment k exemption only on a case-by-case basis.

Those states opting for case-by-case application of comment k typically require a drug manufacturer to carry the burden of proving that a product's benefits outweighed its risks at the time of distribution. Often the focus will be on whether a safer, equally efficacious alternative was available when the plaintiff took the challenged product.

Most courts have held that obtaining FDA approval of a drug does not provide a manufacturer with an absolute shield from state tort liability. Evidence of compliance with FDA warning regulations may be introduced as evidence of the adequacy of such warnings. But manufacturers have been held liable for an inadequate warning even where FDA had expressly refused to approve the addition of the warning owing to a lack of evidence supporting causation.

Courts have also held that FDA approval of a vaccine does not preempt state tort claims. Under federal legislation in effect since 1988, however, certain properly prepared childhood vaccines accompanied by adequate warnings to the medical community can be afforded comment k protection, and there is a rebuttable presumption that warnings in compliance with federal regulations are adequate.
The law regarding preemption of state tort claims as to medical devices differs from that applicable to drugs, in large part because of a specific statutory provision for federal preemption of state laws respecting devices (21 U.S.C. § 360k). At least one court has held that any preemptive effect of the Medical Device Amendments (MDA) are not controlling as to IUDs that are classified as drugs as well as devices. Two courts have split on whether the MDA and federal regulations (21 C.F.R. §§ 808.1(b), (d), and part 813) preempt strict liability claims involving experimental intraocular lenses. In recent months, two federal appellate courts have ruled that state claims are preempted for Class III medical devices that require premarket approval of safety and effectiveness by the FDA under 21 U.S.C. § 360c(a)(1)(C). Because these latter decisions were based on express preemption language in the MDA and related federal regulations, their holdings do not extend to drugs, which are approved under statutory provisions with no comparable preemption language (21 U.S.C. § 355).

Clinical investigators, IRBs, and research institutions would be subject to tort liability under negligence principles. As discussed above, this involves showing that the defendant breached a legal duty owed to the plaintiff and the breach caused an injury to the plaintiff. Bases for liability can include violation of a duty imposed by federal regulations, or violation of the standard of care in the community.

LIABILITY FOR EXCLUDING WOMEN FROM CLINICAL STUDIES

Excluding women from clinical trials has long been viewed as a means of avoiding claims for injuries during the studies, especially potential injuries to offspring. This view appears supported by FDA guidelines on conducting clinical studies, which emphasize the exclusion of "women of childbearing potential." Conformance to FDA guidelines is important protection for establishments and individuals, because "use of testing guidelines established by FDA assures acceptance of a test as scientifically valid," and a "guideline may be used in . . . court proceedings to illustrate acceptable and unacceptable procedures or standards." Thus, FDA and other government guidelines on conducting clinical trials can have an important impact on whether women are included or excluded.

An important consideration in reversing the exclusionary approach is its effect on liability after a drug is marketed. If a drug manufacturer fails to include women in a clinical study, it could face a serious risk of liability if postmarketing evidence indicates that the drug is more dangerous or less effective for women than for men. Such evidence might support a claim that the manufacturer had failed adequately to test the product, arguably rendering the product defectively designed. Such evidence also could support a failure-to-warn claim. The law requires manufacturers to warn
about not only known risks but also foreseeable risks that should have been known if the manufacturer had applied "reasonable, developed human skill and foresight." And if the failure to warn of foreseeable risks was due to the deliberate indifference of the manufacturer - for example, the manufacturer tried to avoid learning whether a likely risk was in fact associated with its product - the manufacturer could be liable for punitive damages (intended to punish or deter) as well as for compensatory damages (intended to compensate losses).

Adequate warnings are required even in those states where comment k applies to all prescriptions drugs. In California, a drug manufacturer is responsible for warning of known risks and those that were "reasonably scientifically knowable at the time of distribution." Similarly, under Utah law, drug manufacturers must warn the medical profession of all risks about which they know or should know. Drug manufacturers are deemed to be experts with a continuing duty to keep up with knowledge in their field.

Similar rules apply in those states that afford drugs and vaccines comment k protection on a case-by-case basis. A vaccine can be found defectively designed if it is not "as safe as the best available testing and research permits." Although "unexpected and unknown risks" will not trigger strict liability, sellers are deemed to be experts and are imputed to have all "knowledge of the product's risks based on reliable and obtainable information." To obtain the benefits of comment k, a medical product "must conform to the highest standards of available scientific and technical knowledge." Such standards include state-of-the-art testing of the product.

Drug manufacturers will likely find it increasingly difficult to prove that all-male studies of many drug products constitute state-of-the-art testing. There is growing recognition that the physiological differences between men and women make it scientifically inadequate in many instances to conduct clinical tests or epidemiological studies using only male subjects. For example, in 1990 Dr. Claude Lenfant, Director of the National Heart, Lung, and Blood Institute, responded to a question about the all-male Multiple Risk Factor Intervention Trials - a study of coronary disease risk factors with the ironic acronym "MR. FIT" - by noting the changing views about the adequacy of all-male testing: "In 1972, it was . . . considered appropriate to have a study using only one gender. Today, I would like to submit to you that that would be viewed to be completely inappropriate." And a recent signed editorial in the Journal of the American Medical Association commented that "data applicable to elderly patients and to women must be derived from the relevant research source: studies conducted in these specific populations."

IRBs and investigators have an obligation to follow FDA and other governmental regulations and guidelines governing their conduct (e.g., 45 C.F.R. pt. 46). For example, IRBs are responsible for assuring that the "]selection of
subjects is equitable." This regulation might be used as the basis for a claim against an IRB that approves a protocol excluding women. The regulation also identifies pregnant women as one of several "vulnerable populations" that require particular consideration by IRBs. If women are deemed vulnerable under this regulation only when they are pregnant, then non-pregnant women are among the classes that should be equitably selected as subjects for a clinical trial. "Scientific design" is among the factors to be considered when determining "whether the selection of subjects is 'equitable.'" However, the preamble to this regulation as revised in 1991 suggests that it was intended to promote the safety of vulnerable populations more than to assure inclusion of nonvulnerable populations.

In sum, a manufacturer must assure that its clinical trials are adequate to satisfy its two legal obligations - (1) its duty to properly design its drug product, and (2) its duty to provide adequate warnings of known and foreseeable risks. To satisfy these legal obligations, the clinical trials must follow scientifically accepted research methods and include informed consent by the study subjects.

LIABILITY FOR INCLUDING WOMEN IN CLINICAL STUDIES

Federal statutes, regulations, and guidelines governing the conduct of clinical studies are designed to minimize the risks of injury to human subjects. For example, clinical studies of drugs and medical devices must comply with FDA requirements (21 C.F.R. pts. 50, 312, and 812). These include: the submission and approval of a study protocol and informed consent by an IRB; the submission of an application to FDA containing pharmacology and toxicology information from studies in laboratory animals or in vitro showing that it is "reasonably safe" to conduct the proposed clinical investigation, as well as information on previous human experience with the product (e.g., from marketing outside the United States); preparation of an investigator's brochure containing information about the product and its effects, possible risks, and precautions; and prompt reporting by investigators and study sponsors of significant safety information arising during the clinical study. Where all of these requirements have been followed, any injury to a subject that does occur is unlikely to result in liability.

One important question is the extent to which warnings and informed consent permit women to be included in clinical studies in the face of information about either foreseeable risks to women in particular or unknown risks. An injured subject conceivably could bring an action based on, for example, failure to test in animals for the then unknown effects that resulted in injury. To the extent that any such liability may be imposed, however, it would involve elements of negligence and informed consent that are not gender specific.
Because of their experimental nature, the products involved in clinical studies are especially strong candidates for comment k protection. This point is noted expressly in comment k itself, where it discusses

new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety . . . but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk.

Provided that the manufacturer warns that the drug is experimental and warns of known and reasonably knowable risks, comment k should apply to an experimental drug.\textsuperscript{42} Of course, should evidence of risks to women develop during clinical trials, manufacturers would be responsible for determining whether to exclude women from further involvement in the trials as well as to warn about the newly discovered risks.\textsuperscript{43}

Investigators testing an experimental drug are likely to be held to the same standards as physicians treating a patient.\textsuperscript{44} Thus, a subject’s probable theories of recovery would be negligence and lack of informed consent.\textsuperscript{45} Federal regulations regarding informed consent prohibit requiring subjects to waive their legal rights.\textsuperscript{46} Investigators and institutions conducting clinical trials therefore are potentially liable for negligence in implementing a clinical study.

IRB members also may be sued under state tort law.\textsuperscript{47} Although IRBs are not primarily responsible for the design of clinical studies, they potentially could be liable for failing to assure that adequate warnings were given to women where evidence existed of particular risks to women.\textsuperscript{48} However, there is apparently no reported case in which IRB members have been successfully sued for breaching their duties to protect research subjects, male or female. The conscientious design and use of informed consent procedures should limit the likelihood that any firm, institution, or individual involved in drug clinical trials would actually be found liable for including women as research subjects.\textsuperscript{49}

**CONCLUSION**

Inclusion of women in clinical studies is unlikely to significantly increase the risk of liability for harm to subjects participating in the clinical trials, while exclusion of women could lead to liability for injuries to women after the product is marketed.
NOTES

1 Federal agencies and employees are protected from suit by the principle of sovereign immunity. The Federal Tort Claims Act provides a limited exception allowing a lawsuit against an agency (not individuals) for injury resulting from negligence in performing "nondiscretionary" acts. 28 U.S.C. §§ 1346(b), 2679, 2680(a). FDA drug regulatory actions pursuant to statute will not be actionable if they involve a permissible exercise of policy discretion. See Berkovitz v. United States, 486 U.S. 531 (1988).


3 There are other possible causes of action, such a fraud and misrepresentation, see, e.g., Allen v. G.D. Searle & Co., 708 F. Supp. 1142, 1160-61 (D. Or. 1989), and contract related claims, such as breach of warranty, see, e.g., Castrignano v. E.R. Squibb & Sons, Inc., 546 A.2d 775, 783 (R.I. 1988). These are beyond the scope of this paper.


5 Restatement (Second) of Torts § 402A. Strict liability claims fall into three categories, mismanufacture, design defect, and failure to warn.


8 Brown v. Superior Court, 751 P.2d 470, 482-83 & n.11 (Cal. 1988); Grundberg, 813 P.2d at 90, 97. Without directly addressing the question of whether comment k applies to all prescription drugs, several other jurisdictions arguably have endorsed such a blanket exemption. See, e.g., McKee v. Moore, 648 P.2d 21, 24 (Okla. 1982) (drug manufacturer strictly liable only if it fails to warn physician adequately).

9 Collins v. Eli Lilly Co., 342 N.W.2d 37, 52 (Wis.) cert. denied, 469 U.S. 826 (1984); Shanks v. Upjohn Co., 835 P.2d 1189, 1197-98 (Alaska 1992). While declining to adopt comment k itself, the court in Shanks did indicate that drug manufacturers could raise as an affirmative defense to a strict liability design defect claim the type of risk/benefit analysis that many courts use in deciding whether to grant a drug comment k protection. Id. at 1996-98.
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11 E.g., Toner, 732 P.2d at 306-07.

12 See, e.g., id. at 306; Adams, 576 So. 2d at 732.33. But see Harwell v. American Med. Sys., 803 F. Supp. 1287, 1297, 1300 (M.D. Tenn. 1992) (under Tennessee law, prescription medical device can be deemed unavoidably unsafe without proof that no safe alternative was available).


14 Savina, 795 P.2d at 931; Feldman II, 592 A.2d at 1197.


17 42 U.S.C. §§ 300aa-22(b), (c) (1988); see H.R. Rep. No. 100-391 (I), 100th Cong., 1st Sess. 691 (1987); Abbot, 844 F.2d at 1117 (Wilkins, J., concurring).


20 Stamps v. Collagen Corp., No. 92-2084 (5th Cir. Feb. 19, 1993); King v. Collagen Corp., No. 92-1278 (1st Cir. Jan. 15, 1993). Cf. Moore v. Kimberly-Clark, 867 F.2d 243, 246-47 (5th Cir. 1989) (holding that failure-to-warn and labeling claims were preempted for Class II device, which does not require premarket approval, but defective construction and design claims not preempted). But cf. Larsen v. Pacesetter Sys., Inc., 837 P.2d 1273, 1282 (Haw. 1992) (declining to find preemption regarding a Class III device that underwent a less rigorous premarket approval process than the devices involved in the Collagen cases because the Larsen device was " 'substantially equivalent' " to devices already approved for marketing).

21 See Stamps, slip op. at 6-8 + n.1; King, slip op. at 8-10.

22 E.g., Gaston, 588 P.2d at 346, 350-51. Depending on state law, specialists may be held to a national standard of care. See id. at 346. If an investigator were deemed a specialist, the investigator would be held to " ' the standard of care required of physicians in the same specialty. . . . ' " Id. (quoting Kronke v. Danielson, 499 P.2d 156, 159 (Ariz. 1972)). A physician/investigator's responsibilities include obtaining the subject's informed consent. Id. at 350-51.
23 FDA, General Considerations for the Clinical Evaluation of Drugs 10 (September 1977) (DHEW/FDA Pub. 77-3040).


25 Restatement (Second) of Torts § 402A comment j. See, e.g., Shanks, 835 P.2d at 1200 (indicating that, under strict liability failure-to-warn claim, the defendant must "prove that the risk was scientifically unknowable at the time the product was distributed to the plaintiff"); Feldman I, 479 A.2d at 388 (similar).

26 Brown, 751 P.2d at 483.

27 Grundberg, 813 P.2d at 97. See also Enright v. Eli Lilly & Co., 568 N.Y.S.2d 550, 556 (drug manufacturers are not immune "from liability stemming from their failure to conduct adequate research and testing prior to the marketing of their products") (dictum), cert. denied, 112 S. Ct. 197 (1991).

28 Grundberg, 813 P.2d at 98.

29 Toner, 732 P.2d at 306.

30 Id. at 307 (citing Feldman I, 479 A.2d at 386-87; Belle Bonfils Memorial Blood Bank v. Hansen, 665 P.2d 118, 126 (Colo. 1983)).

31 Belle Bonfils, 665 P.2d at 126.

32 See id. at 125, 127. Cf. Feldman I, 479 A.2d at 386-87 (indicating that drug manufacturers may have duty to continue testing after product first approved). The value of having an extensive data base regarding a drug's safety when defending against product liability actions is suggested in Daubert v. Merrell Dow Pharm., Inc., 951 F.2d 1128, 1129 (9th Cir. 1991) (noting defendant's citation of "30 published studies involving over 130,000 patients"), cert. granted, 113 S. Ct. 320 (1992).

33 See, e.g., Jean Hamilton (ed.), Clinical Pharmacology Panel Report 1, in Susan J. Blumenthal et al. (eds.), Forging a Women's Health Research Agenda, Conference Proceedings, National Women's Health Resource Center (Washington, D.C. October 1991) ("Despite the lack of systematic study in the past, clinically significant sex, hormone or gender-related effects have been reported for the following drugs or types of drugs: antidepressants (e.g., lithium), antidopaminergic antipsychotics, anticonvulsants (e.g., phenytoin), an antihypertensive (propranolol), several sedative-hypnotics (e.g., diazepam; methaqualone), alcohol, and possibly for insulin, synthetic glucocorticoids, theophylline, and caffeine. A 'clinically significant effect' is that having implications for altering decisions about pharmacotherapy for women, not just findings that reach statistical significance.")

Id. at 286. Other observers have questioned a study of the long-term use of aspirin to help prevent myocardial infarction because the study involved only men and left unclear whether the benefits observed for men would apply to women as well. See, e.g., L. Elizabeth Bowles, *The Disfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap*, 45 Vand. L. Rev. 877, 887-88 (1992). Although later studies indicated an apparent beneficial effect for women, see id. at 888 (citing Lawrence Appel and Trudy Bush, *Preventing Heart Disease in Women: Another Role for Aspirin*, 266 JAMA 565 (1991)); *NIH Reauthorization: Hearings Before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce*, 102d Cong., 1st Sess. 233 (1991) (testimony of Dr. Bernardine Healy), the Director of the National Institutes of Health, Dr. Bernardine Healy, acknowledged as recently as 1991 that it was still unclear whether "aspirin poses a unique danger for women." Id. Dr. Healy indicated opposition to proposed legislation that would have required the inclusion of women in NIH-sponsored clinical studies absent a showing that such inclusion was inappropriate. See id. at 232. She noted, however, that similar guidelines were already NIH policy and that the proposed legislation thus was not necessary. Id.


*Id.*


See Gaston, 588 P.2d at 340. See also Toner, 732 P.2d at 307 (noting comment k's specific discussion of experimental drugs). The *Gaston* court also declined to treat drug experiments as abnormally dangerous activities and thus refused to impose the even harsher regime of absolute liability on either investigators or manufacturers. 588 P.2nd at 341-42. The court based its decision in part on the rationale that the law regarding absolute liability does not apply to those who voluntarily engage in the activity. *Id.* at 341. *See also Whitlock v. Duke Univ.*, 637 F. Supp 1463, 1475-76 (M.D.N.C. 1986) (rejecting similar claim in case involving non-therapeutic experiment), aff’d per curiam, 829 F.2nd 1340 (4th Cir. 1987).

See, e.g., *Feldman I*, 479 A.2d at 386-87.

E.g., *Gaston*, 588 P.2d at 346, 350-51.
See, e.g., Valenti v. Prudden, 397 N.Y.S.2d 181 (App. Div. 1977) (prison inmate voluntarily involved in non-therapeutic surgical experiment brought claims for negligence and lack of informed consent against hospital and doctor). See also Anderson v. George H. Lanier Mem'l Hosp., 1993 U.S. App. LEXIS 2161, at *18-20 (11th Cir. Feb. 12, 1992) (although related malpractice claims were barred by statute of limitation, hospital at which investigational devices installed is potentially liable for fraud due to physician's alleged failure to obtain informed consent); Friter v. Iolab Corp., 607 A.2d 1111 (Pa. Super. 1992) (hospital conducting clinical study of investigational device can be held liable for battery and failure to assure that physician obtained informed consent required under federal regulations; plaintiff had already settled with physician's representatives). Cf. Tracy, 569 N.E.2d at 879-80 (holding that learned intermediary rule applies in investigational context when investigator determines subject's suitability for inclusion and monitors subject's involvement). Because the Tracy court focussed on whether the investigator acted as a treating physician would, there is some question whether its holding would apply in cases involving subjects whose involvement in a clinical trial was entirely non-treatment oriented.


See generally id. ("[T]he primary responsibilities of an IRB are to assure that human subjects are adequately protected, are not exposed to unnecessary risks, and are provided with enough information about a study so that they can give effective informed consent. However, the agency believes that it is impossible to divorce completely considerations of science from those of ethical acceptability and of protection of human subject. Some type of scientific review is necessary to determine whether the risk to which subjects are exposed is reasonable.")

See, e.g., id.