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Tort Reform to Ensure the Inclusion of Fertile Women in Early Phases of Commercial Drug Research

SUSAN EPSTEIN

The vast majority of prescription and non-prescription drugs are not tested on women. The leading analyses of published clinical trials have indicated that there has been little or no inclusion of women, in particular fertile women, as subjects in many of the drug studies. This exclusion would not be problematic if women and men responded to all drugs in the same way. However, growing medical knowledge indicates that drugs react differently in men's

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There are many groups, in addition to women, that have been excluded from medical research or for whom data has also not been analyzed. The exclusion of these groups is no more justified scientifically or ethically. Responses to drugs are influenced by many factors, including age, sex, and ethnic background. See Ruth B. Merkatz, et al, Women in Clinical Trials of New Drugs: A Change in Food and Drug Administration Policy, 329 New Eng J Med 292, 292 (1993). Many of the issues are similar and there is substantial overlap in the constituencies. Ethnic differences in drug responses are also becoming more well known. Paul Cotton, Examples Abound of Gaps in Medical Knowledge Because of Groups Excluded from Scientific Study, 263 JAMA 1051, 1051 (1990) (“Examples Abound of Gaps”). Only recently have some researchers begun to find pharmacokinetic explanations for these differences. Id. Gaps remain despite increasing documentation of these differences and risk profiles among non-whites. Paul Cotton, Is There Still Too Much Extrapolation From Data on Middle-aged White Men?, 263 JAMA 1049, 1049 (1990) (“Extrapolation”). Some African- and Asian-American researchers are seeking a grant for a multietnic research center. Id. Community-based research may be a solution to the problem of centuries of mistrust of the very institutions that are trying to now recruit minority subjects. This mistrust was born of historical incidents such as the infamous Tuskegee Institute experiment conducted in Alabama in the 1930s: scientists deliberately left syphilis untreated in African-American men. Id at 1050. The elderly comprise another group whose exclusion from medical research has been discussed frequently in medical literature in the past decade. Id.

2. 58 Fed Reg at 39406 (cited in note 1).
and women's bodies; many studies have shown that fertile women in particular respond differently than men to some drugs. Gender-related differences in response to drugs can arise from pharmacokinetic differences or pharmacodynamic differences. Pharmacokinetic responses refer to the way a drug is absorbed, excreted, metabolized, or distributed. Pharmacodynamic responses are the pharmacologic or clinical reactions to a given concentration of the drug in blood or other tissue.

Whether drugs may react differently in men and women can be determined during early phases of drug testing. Such testing would ensure that drugs are safe and effective for both sexes. Nevertheless, pharmaceutical manufacturers exclude women from early phases of drug testing, endangering women who eventually take those drugs.

The goal of this Comment is to demonstrate how litigation can be used to modify the behavior of pharmaceutical manufacturers, and how the prohibitive cost of litigation can be reduced for women who have been injured by drugs not tested on women. Currently, if an injured woman sues a manufacturer for not testing the drug on women, she must prove both that the drug should have been tested on women and that the drug caused the injury because it was not tested on women. Because the injured woman presumably does not have a laboratory or the financial resources to study and prove this causation, her claim will be dismissed for failure to state a cause of action. This Comment proposes that state courts or state legislatures adopt a rebuttable presumption that a pharmaceutical defendant's lack of testing is the cause of the woman's injury—with a correspondingly shifted burden of proof.

Section I of this Comment summarizes the growing medical understanding of differences in responses to drugs and of the possible harm to women excluded from clinical trials, particularly early phases of studies. This Section explains the reasons women have been excluded from clinical trials. Section II addresses whether those reasons justify exclusion. Section III proposes that litigation be brought, or threatened, by women who have been injured by drugs not tested on women. Because the main legal difficulty facing a plaintiff in such suits is proving the element of causation, this Comment proposes that courts shift the burden of proof and create a rebuttable presumption that the defendant manufacturer's drug caused the plaintiff's injury.

In Section IV this Comment will explain why a litigation approach is both necessary and likely to be effective. Section IV will also discuss circumstances where such rebuttable presumptions and shifted burdens are appropriate in the legal system, and why these women's drug product liability suits are appropriate in light of legal, ethical, and scientific policy considerations.

4. 58 Fed Reg at 39409 (cited in note 1).
5. Id.
6. Id.
7. See notes 149-53 and accompanying text.
I. Current Commercial Medical Research Practices

Fertile women have been excluded from medical research, in particular from early phases of clinical trials, despite growing medical understanding of differences in the way drugs react in women's and men's bodies. “[D]ifferences between the sexes in responses to drugs and other interventions are being reported more frequently.” Studies already have found, for example, that some benzodiazepines remain in the bodies of women longer than in men. Similarly, women metabolize alcohol, ondansetron, lidocaine, aspirin, and mephobarbital more slowly.” This increasing evidence reveals that differences in drug reactions between women and men occur due to variations in body fat, muscle mass, hormonal conditions, and other factors. “Biologic differences between men and women may reflect genetic, physiologic, lifestyle, cultural, and social differences—although the mechanisms that explain these differences are to a great extent unknown.” The FDA is aware of these studies and of the corresponding need to test drugs on women as well as men.”

Drugs are tested in three phases. In phase 1, a scientific screening can

10. AMA Response at 2 (cited in note 8).
11. 58 Fed Reg at 39407 (cited in note 1); Merkatz, 329 New Eng J Med at 293 (cited in note 1).
Concerns about the adequacy of data on the effects of drugs in women have arisen at a time when the FDA, drug developers, and the scientific community have focused increasingly on the need to individualize treatment in the face of the wide variety of demographic, disease-related, and individual patient-related factors that can lead to different responses to drugs in subsets of the population. Optimal use of drugs requires identification of those factors so that appropriate adjustments in dose, concomitant therapy, or monitoring can be made. Subgroup-specific differences in response can arise because of variation in a drug's pharmacokinetics... or pharmacodynamics. ...

Id. With regard to pharmacokinetics, the notice stated that “small body size or muscle mass may lead to higher blood concentrations after a given dose.” See also Merkatz, 329 New Eng J Med at 294 (cited in note 1).
15. Phase 1 refers to the first introduction of a new drug into humans, who are often, but not always, healthy volunteers, to study the basic tolerability of the drug, its metabolism, and its short-term pharmacokinetics. Merkatz, 329 New Eng J Med at 293 (cited in note 1). Phase 1 studies generally involve small numbers of subjects. Id. Phase 1 studies, however, may also provide preliminary pharmacologic information related to
be performed to determine if women and men may react differently to the
drug being tested. This screening is based on (1) the results of studies of
human subjects conducted in phase 1, and (2) existing data such as animal
studies, toxicology studies, and available scientific knowledge of the substances
in the drugs and their effects in humans. If a potential gender difference exists,
women and men can then both be studied in large numbers during phase 2
and phase 3 to ensure that the drug is safe for both sexes and that the drug
is sold in appropriate dosages and concentrations. This method of screening
for gender-related differences during phase 1 and including women or men in
large numbers during phase 2 and 3 studies, depending on the results of the
phase 1 screen, is recommended by the Food and Drug Administration
(“FDA”) in a 1993 guideline.16 Because the FDA guideline is not mandatory,
pharmaceutical companies are not changing their drug testing procedures.17
Women, and especially fertile women, are still being excluded from drug
testing and particularly from phase 1 testing.18

A. INDUSTRY STANDARDS AND JUSTIFICATIONS FOR EXCLUSION OF WOMEN

“[W]omen generally have not been included in phase 1 nontherapeutic
studies or in the earliest controlled effectiveness studies (i.e. early phase 2
studies).”19 Paradoxically, a 1977 FDA guideline explicitly required their
exclusion. The guideline stated that, “in general, women of childbearing potential
should be excluded from the earliest studies of a new drug, that is, phase 1 and
early phase 2 studies.”20

Even where women are included in phase 3 studies, few analyses of the data
are conducted to detect possible differences in effectiveness or safety between
men and women.21 “Although women have been included in the later phases of
some clinical trials, inclusion alone is not sufficient for adequate assessment of
potential gender differences.”22

Recently, however, the FDA reformed its policy of exclusion. A 1988 FDA
guideline urged all new drug applications (“NDAs”) to analyze gender-related

clinical effectiveness and relative safety. Id. Phase 2 refers to the initial controlled trials of
a drug to study its effectiveness. Before the first such study, there is generally no evidence
that the drug is of therapeutic value in humans. Id. Phase 2 studies normally involve a
few hundred patients. Id. “During Phase 3, the final testing phase before a marketing
application is submitted to the FDA for review, as many as several thousand patients are
studied. These studies provide additional evidence regarding safety and effectiveness, in-
cluding data on long-term exposure; refine information on dose-response and concentra-
tion-response relations; and identify relatively rare adverse effects.” Id.

16. 58 Fed Reg at 39409-10 (cited in note 1).
17. See text accompanying notes 191-93.
18. See text accompanying notes 194-96.
19. 58 Fed Reg at 39408 (cited in note 1).
20. Id at 39407.
22. 58 Fed Reg at 39407 (cited in note 1).
differences. The "FDA and GAO examined NDAs to see whether analyses of this kind were being conducted and submitted. Both examinations found that in many cases (about half) the databases were not being analyzed to determine whether there were gender, age, or race differences in response to drugs." In 1993 the FDA released a new guideline recommending, but not requiring, that women be included in phase 1 studies and also be included in large numbers in later phases when it is scientifically plausible that women will react differently to the drug.

Nonetheless, many pharmaceutical companies have not yet designed trials tailored to test the relation between gender and drug reactions. "Despite the many examples of documented pharmacokinetic and pharmacodynamic differences in population subsets, there ... [remains] insufficient attention in the course of drug development to looking for such differences among individuals in responses to drugs, including differences related to gender." Also, there has been little study of the effects of aspects of female physiology, such as the menstrual cycle and menopause, on drug action and pharmacokinetics, even with respect to drugs widely used by women. Use of oral contraceptives, systemic progestins and estrogens, concomitant oral contraceptive or estrogen use, differences based on different body fat proportions, and differences in weight or muscle mass all require more extensive study.

A striking example of researchers overlooking women occurred in the design of antidepressants. Although evidence pointed to women having much higher rates of clinical depression, the initial research on antidepressants was conducted entirely on men. Since these antidepressants have been placed on the market, evidence has emerged that the need for antidepressants may vary over the course of a woman's monthly cycle. These studies suggest that a varied dosage during the month may be more appropriate than a constant dosage.

In addition to the 1977 FDA guideline, there are three major reasons why women have been excluded: (1) researchers minimize costs by choosing to study a homogenous group—middle-aged white men; (2) researchers do not want to injure women subjects or fetuses; and (3) researchers fear litigation by these women subjects or their children.

Researchers have preferred to study a homogenous group of middle-aged white men primarily because, in any scientific study, it is best to have few

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23. Id.
24. Id.
25. Id at 39409-11.
26. Id at 39407.
27. Id.
28. Id.
29. Id at 39406-07.
31. Id.
32. Id.
variables so that you can focus on only those variables you are testing. Gender, race, socio-economic status, and age are seen as "confounding variables."\(^3\)

Another reason to study a homogenous group is that additional variables are more expensive and time-consuming; both hurt the bottom line, and pharmaceutical companies must compete in the market. It is less expensive and faster to study one group.\(^4\) Furthermore, since all people are more alike than not, it is easier to justify studying just one subgroup.\(^5\) Also, if researchers are fairly sure that there will be no biological differences between men and women with regard to reactions to a particular drug, they are quick to study just men.\(^6\) The Pharmaceutical Manufacturers Association ("PMA")\(^7\) has recently argued against including women in all clinical trials.\(^8\) Researchers are concerned that stringent rules on trial design, requiring the inclusion of every imaginable subgroup of humans, will hinder the release of the drug product. “[A]t some point drug companies ‘just won't bother if the requirements are so expensive.’”\(^9\) These concerns about cost are particularly strong in light of the scientific need to include large numbers of members of subgroups to detect significant differences among the subgroups. Even different subgroups of women have different responses to therapy.\(^10\) The final reason to study homogenous groups of middle-aged white men is that those designing the studies are overwhelmingly middle-aged white men and, perhaps subconsciously, are most concerned with medical problems they may face themselves.\(^11\)

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33. Marcia Angell, *Caring for Women’s Health: What is the Problem?*, 329 New Eng J Med 271, 271 (1993). See also *Extrapolation* at 1049 (cited in note 1) (“A myopic view of confounding factors in clinical research is continuing to confound clinical practice. Efforts to streamline studies by using the most homogenous population possible have filled medical libraries with data on middle-aged white men. Even female rats are commonly excluded from basic research.”).

34. See Bennett, 329 New Eng J Med at 290 (cited in note 9) (“The high cost and complexity of large-group trials prohibit their performance except in common diseases.”).


36. Id.

37. PMA is a trade association representing more than 100 companies engaged in the research, development, manufacture, and marketing of prescription pharmaceutical and biological products.

38. John D. Siegfried (representing the PMA), Letter to the FDA, *Comments on FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* 2 (Nov 19, 1993) (“PMA Response”) (on file with the University of Chicago Law School Roundtable) (“The need for larger trials, additional pharmacokinetic studies, conduct of animal studies earlier, and conduct of animal studies in drugs that ultimately are not developed, all contribute to higher drug development costs at a time when Congress and the current Administration are searching for cost containment and reduction in healthcare spending.”).


41. See *Extrapolation* at 1050 (cited in note 1) (“The notion that white men present fewer confounding factors is ‘an assumption made very glibly, and only because white men run the country,’ says Jerry Avorn, M.D., a geriatrician and associate professor of social
Whether discrimination is subconscious or not, the conclusion that men are simpler to study is based on some odd assumptions. For example, a recent article in a medical journal stated that men have "more readily identifiable cohorts" with which to compare study results, citing army veterans as an example. This argument is not particularly persuasive—traditional female groups like secretarial pools, of course, provide similar cohorts.

The second major reason often cited for exclusion of women is that researchers do not want to injure women subjects or fetuses. The original reason that the FDA's 1977 guideline excluded all women of childbearing potential from clinical trials was fear of injury to female subjects' reproductive capacities and fear of injury to any potential fetuses that women subjects might conceive. These remain concerns of those who argue that fertile women should continue to be excluded.

A third major reason for exclusion of women is the fear of litigation. A PMA representative recently stated, "There is always a possibility of pregnancy and damage to a fetus. In the current legal climate, a fetus would have a legal right until age 21 against the sponsor." When drug companies do include female subjects in their research, they recruit surgically sterilized women. The fear of possible harm to a potential fetus, combined with increased political pressure to include women in clinical trials, seems to have scared many drug companies into testing only surgically sterilized and post-menopausal women and sometimes only in phase 3. In one reported case, where research was conducted on a drug that would be prescribed only to fertile women, the pharmaceutical company tested the drug on no fertile women.

medicine at Harvard University Medical School, Boston, Mass."). See also Janny Scott, Susan Love: Setting the Agenda for the Politics of Breast Cancer, LA Times M3 (Dec 5, 1993) (Susan Love, a breast cancer activist, recently stated, "I don't think the researchers are misogynists; I think if you're sitting there with a small pot of money, you will spend it on what you fear. And if you're a middle-aged white male, it's more likely to go to heart disease than breast cancer.").

42. Bennett, 329 New Eng J Med at 289 (cited in note 9).

43. Paul Cotton, Women's Health Initiative Leads Way as Research Begins to Fill Gender Gaps, 267 JAMA 469, 470 (1992) (Lionel Edwards, chair of PMA's special populations committee, stated, "A blanket inclusion of women in every study would put them and their unborn children at unnecessary risk. . ."). See also PMA Response at 2 (cited in note 38).

44. Telephone Interview with John Siegfried, M.D., representative of the PMA (Jan 1994).

45. The PMA released the results of a survey in December 1991; 33 of 46 companies that the PMA surveyed responded. 76% said they deliberately recruit representative numbers of women for trials. Cotton, 267 JAMA at 470 (cited in note 43). In a November 1993 letter, however, a PMA representative wrote, "In circumstances where the potential risk is greater than the benefit of the information likely to be gained, post-menopausal and surgically-sterilized women can be studied in the earliest trials. Some PMA sponsors have actively recruited this population for several years to increase women's participation in early research." PMA Response at 2 (cited in note 38).

46. Joan O'C. Hamilton and Peter Hong, When Medical Research is For Men Only,
B. HARM TO WOMEN

The harm resulting from women's exclusion is enormous. “Women not only use more prescription drugs than men but suffer proportionately more adverse drug reactions, even when controlling for dose and number of drugs prescribed.”\(^4\) The FDA's explicit exclusion in its 1977 guideline of women of childbearing potential from early clinical trials led to a "general lack of participation of women in drug development studies, and thus to a paucity of information about the effects of drugs in women."\(^4\) This lack of information or indefinite information creates extrapolation concerns. Scientists and doctors are uncertain whether to recommend drugs for women when those drugs have been tested only on men.\(^4\) The doctors may wonder whether the drugs will be effective and safe for a female patient.\(^5\)

Women's exclusion from studies of cardiovascular disease has been particularly tragic. "Heart disease has been the leading killer of American women since 1908."\(^5\) Women will comprise nearly half of the 500,000 Americans who die of heart attacks this year.\(^5\) Nevertheless, until recently, practically no studies on cardiovascular disease have included women subjects, and even now very few of these studies include women.\(^5\) As a result of the lack of clinical information about women and cardiovascular disease, there is "insufficient information about preventive strategies, diagnostic testing, responses to medical and surgical therapies, and other aspects of cardiovascular illness in women."\(^5\)

Exclusion also harms the increasing number of women aware of the inequity in drug testing and effects, who then fear taking untested drugs and distrust the medical profession.\(^5\) This is dangerous both for women patients and for wom-

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3169 Bus Wk 33, 33 (July 16, 1990) (“Restricting a drug's use to half the population is bad for the bottom line. . . . Genentech Inc. didn't let reproductive safety concerns short-circuit research on Relaxin, a hormone that could ease childbirth. Its safety profile is being analyzed in a group of surgically sterilized women.”).

48. 58 Fed Reg at 39406 (cited in note 1).
49. Extrapolation at 1049 (cited in note 1); Angell, 329 New Eng J Med at 271 (cited in note 33).
50. Extrapolation at 1049 (cited in note 1).
52. Id.
55. Andrea P. Graham, Introduction, Harv Med Sch Women's Health Watch News 1 (1993) ("If women's bodies responded to medications the way men's do, then we could feel confident taking drugs tested only on men. But nearly all drug testing (including the role of estrogen in heart disease!) has been done only on men. If men and women faced identical risks, then we could safely undergo surgical procedures proven effective only on
en in the medical profession. The FDA's explicit exclusion of women of child-bearing potential from clinical trials in its 1977 guideline "also may have perpetuated . . . a view of the male as the primary focus of medicine and drug development, with women considered secondarily."56 For example, fertile women are often excluded because the menstrual cycle is seen as a confounding factor57 but since fertile women are expected to use the drugs, the message given by the exclusion is that safety is the purpose of drug testing, but only in regard to men.

Not only are women harmed by drugs never tested on women, but they are especially harmed by the exclusion of fertile women from early phases of clinical trials. During phase 1 the development of the drug is adjusted based on the subjects' reactions. If women were included in phase 1 studies, drugs would likely be developed to be more effective and safe for women. "There is reason to believe that earlier participation of women in studies would increase the likelihood that gender-specific data might be used to make appropriate adjustments in larger clinical studies (e.g., different doses in women or weight adjusted dosing . . . instead of fixed doses)."58

"Although the 1977 guideline has not resulted in [an absolute failure] to include adequate numbers of women in the later phases of clinical trials, it has restricted the early accumulation of information about response to drugs in women that could be utilized in designing phase 2 and 3 trials, and has delayed appreciation of gender-related variation in drug effects."59 Another reason that including women in early phases is more important than their inclusion in later phases is that differences in the way the drug behaves in women will be clearer; significant gender differences may appear to be just "noise" in the data from the larger studies during phase 3.60

II. Critique of Current Practices

Given the extent of harm women suffer as a result of exclusion from medical research, the arguments justifying exclusion would have to be extremely compelling. The arguments against including women, however, are far from compelling. Indeed, many of the researchers' arguments against including women are inaccu-

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56. 58 Fed Reg at 39408 (cited in note 1).
57. Extrapolation at 1049 (cited in note 1).
58. 58 Fed Reg at 39408 (cited in note 1).
59. Id. Some women's advocates have argued that it is most important to include large numbers of women in late phase 2 and phase 3 studies to detect any unforeseen adverse effects in women. Vanessa Merton, for example, has argued that pharmaceutical companies should be required to include women in later phases of clinical trials because of therapeutic benefits to subjects. Vanessa Merton, The Exclusion of Pregnant, Pregnable, and Once-Pregnable People (a.k.a. Women) From Biomedical Research 15 (Nov 1993) (unpublished article on file with author).
rate, misguided, and illogical.

The first major reason cited for exclusion—researchers' desire to minimize costs by studying a homogenous group—is misguided. Pharmaceutical manufacturers argue that in order to keep costs down, they must study one homogenous group. There is no rationale, however, for why it must always be the same group. There is no scientific reason for middle-aged white men to be the baseline.

The manufacturers are justified in their concern about greatly increased costs if they have to include every subgroup in large numbers to detect any differences in drug reaction among subgroups. This Comment, however, is not advocating that large numbers of women be included in every clinical trial; rather, women should be included when it is scientifically necessary.

If, as drug manufacturers argue, they must study homogenous groups, then they should alternate which subgroups are studied. Then, the middle-aged white men subgroup might only be studied every tenth drug, for instance. Such a system would lead the pharmaceutical companies, which are overwhelmingly run by middle-aged white men, either to find that the costs of including all the subgroups are not prohibitive or to find a scientific rationale for including large numbers of members of subgroups when necessary and a demographically diverse base otherwise.

Indeed, this Comment argues for including women in equal numbers to men in phase 1 trials and including women in larger numbers in phase 2 or 3 trials only when results from phase 1 indicate the need. This system would not be much more expensive than the current system. The additional cost of developing drugs might lead to a slightly smaller number of drugs being developed each year, but those drugs that were developed would be safer and more effective. The cost to society of less innovation for middle-aged white men is outweighed by the benefit of better drugs for more of the population.

The second major reason cited for exclusion—researchers do not want to injure women subjects or fetuses—may be well-intentioned, but it is also very misguided. For example, this protection rests on the assumption that only women's behaviors and consumptions can cause birth defects. Medical evidence, however, demonstrates that sperm can and has contributed to birth defects. Studies have conclusively shown that sperm can cause adverse reproductive effects, including birth defects. The exclusion of fertile women premised on

61. See note 38.
62. The proposed method of including women when it is scientifically necessary may also apply to other subgroups on whom drugs have typically not been tested, in which case the costs of drug development would not be unreasonably high; the appropriate inclusion of other subgroups is beyond the scope of this Comment.
63. This method of inclusion is suggested throughout this Comment. Also, the 1993 FDA guideline recommends including both males and females in drug study groups. 58 Fed Reg at 39406-11 (cited in note 1).
64. Felissa L. Cohen, Paternal Contributions to Birth Defects, 21 Nursing Clinics N Am 49, 49-51 (1986) (Sperm may contribute to adverse reproductive outcomes including birth defects. The causes include damage to the sperm or male germ cells or alterations in the seminal fluid. These may result from paternal exposure to a chemical, drug,
concerns about harm to potential fetuses is outrageous given the fact that fertile males are equally capable of causing harm to a fetus.

Most paternal contributions to birth defects occur before conception. Clearly, a drug company's research could harm a potential fetus through a male subject. So, if the drug companies' goal in excluding women is to prevent injury to a fetus, they would also have to confine their subject population to irreversibly sterilized men. Indeed, pharmaceutical companies are currently exposing themselves to potential liability because the male subjects are never asked to give informed consent on the basis of possible risk to their future children and are never asked to avoid conception during the course of the trials.

Furthermore, harm to fetuses may be eliminated or lessened by precautions taken against conception while on protocol; the possible harm to a fetus is outweighed by the definite harm to women created by exclusion from clinical trials. "[E]xclusion of women from early trials is not medically necessary because the risk of fetal exposure can be minimized by patient behavior and laboratory testing." Both the AMA and the FDA have stated that banning women's participation in early clinical trials is no longer reasonable or legally defensible.

The PMA, however, does not feel comfortable relying on precautions: "[N]o matter how well a woman understands the risks, legal liability either as a result of inadvertent fetal exposure or possibly from an undetected long term adverse effect on a future pregnancy, remains a very substantial concern." Again, the PMA's concerns are misguided in that they only feel uncomfortable relying on precautions with regard to female subjects, when precautions could fail with male subjects as well, and pharmaceutical companies typically don't even recommend precautions to their male subjects.

Unless pharmaceutical companies plan to only test surgically sterilized subjects of either sex, the researchers will need to recommend precautions against conception to all their subjects of reproductive capacity. These precautions should include (1) advising all subjects of the risk of potential fetuses being exposed to toxic agents, (2) recommending the use of contraceptives, and (3) infectious organism, or other environmental factor. Impaired fertility, infertility, spontaneous abortion, congenital abnormalities, altered fetal growth, postnatal functional deficits, prenatal or perinatal fetal death, or carcinogenesis can all be caused by mutations.) See also Lester F. Soyka and Justin M. Joffee, Male Mediated Drug Effects on Offspring, in Richard Schwarz and Sumner Yaffe, eds, Drug and Chemical Risks to the Fetus and Newborn 49 (Liss, 1980) (describing over 30 medical studies showing that male sperm has contributed or may contribute to birth defects).

67. Id at 66-67.
68. 58 Fed Reg at 39408 (cited in note 1).
69. AMA Response at 2 (cited in note 8); see also Merkatz, 329 New Eng J Med at 295 (cited in note 1).
70. PMA Response at 2 (cited in note 38).
providing an informed consent document and an investigator's brochure with more information on the potential risks.\textsuperscript{71} Other precautions include abstinence, pregnancy testing before and during the trial, and exposure coinciding with or immediately following menstruation.\textsuperscript{72} Special precautions may be needed where animal studies have shown a high chance of adverse reproductive outcomes from the drug.\textsuperscript{73}

These precautions should allow pharmaceutical companies to stop worrying about harm to fetuses. If a drug company takes all reasonable precautions and a subject experiences contraceptive failure, conceives, decides to continue the pregnancy, and gives birth to an affected child, it is unlikely a court would find the drug company liable. "[T]here is no precedent for imposition of liability for harm to a subject's children on a researcher who obtained properly informed consent from the subject."\textsuperscript{74}

The pharmaceutical companies' concern that women subjects might get hurt because clinical trials entail risks is also illogical. Many more women are likely to be harmed when untested drugs are on the market than the few women who voluntarily decide to join a clinical trial.

Researchers have often cited their concern about harming a woman's reproductive capacity.\textsuperscript{75} A woman's reproductive capacity, however, is one of the main reasons why drugs should be tested on women; women's menstrual cycles impact the way medications and other therapeutic interventions react in their bodies.\textsuperscript{76}

\textsuperscript{71} 58 Fed Reg at 39411 (cited in note 1). Whether informed consent should absolve the researcher from liability has been debated. Compare Merton, \textit{Exclusion of Pregnant, Pregnable, and Once-Pregnable People} at 105-11 (cited in note 59) (arguing that sponsors are the cheapest cost avoiders so they owe the subject and should be willing to take on this liability) with Hayley Gorenberg and Amanda White, \textit{Off the Pedestal and Into the Arena: Toward Including Women in Experimental Protocols}, 19 NYU Rev L & Soc Change 205, 229 (1991/1992) (arguing that there should be a public compensation fund instead of sponsor liability because the public good that results from research outweighs the individual's harm).

\textsuperscript{72} 58 Fed Reg at 39411 (cited in note 1).

\textsuperscript{73} Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative treatment, and the duration of therapy.

\textsuperscript{74} Merton, \textit{Exclusion of Pregnant, Pregnable, and Once-Pregnable People} at 65 (cited in note 59).

\textsuperscript{75} AMA Council, 266 JAMA at 559 (cited in note 30).

\textsuperscript{76} Id. See also Cotton, 267 JAMA at 470 (cited in note 43) (Irma Mebane, an epidemiologist at the National Heart, Lung, and Blood Institute, said, "The reality ... is that much of the research that excludes women in their childbearing years, generally [women ages] 15 to 44, winds up affecting these same women. We are de facto saying results are generalizable to them without their being involved in the trial.").
In addition, the exclusion of women from clinical trials rests on a paternalistic assumption that a woman cannot make decisions regarding her own health, safety, and risks. If researchers are concerned about potential fetuses, the researchers do not trust that women as parents can make decisions regarding their children. In addition, researchers assume that if a woman “experiences a contraceptive failure and conceives, she cannot responsibly and intelligently weigh the available information and decide whether to continue or terminate the pregnancy.” The FDA has recognized this paternalism and released its new guideline hoping to remedy it in the future.

Thus, the exclusion of women cannot be justified based on concerns about harms to women or to fetuses. Exposing male subjects to toxic agents may also harm fetuses. Precautions may be taken to prevent both male and female subjects from exposing fetuses. Many more women may be injured when they buy untested drugs than the few who volunteer to join a clinical trial. Finally, restricting only women from participating in clinical trials betrays a paternalistic lack of respect for women's autonomy and decision-making capacity.

The pharmaceutical companies' third major reason for excluding women—fear of litigation by subjects or their children—is misplaced. First, pharmaceutical companies are as likely to be sued many years later by male subjects' children as by female subjects' children. As discussed above, exposing male subjects to toxic agents may also harm fetuses. And a male subject's child is more likely to sue than a female subject's child because a male subject is not asked to give informed consent based on potential harm to a fetus he later

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Extrapolation at 1050 (cited in note 1) (Sidney Wolfe, M.D., of Public Citizens' Health Research Group in Washington, D.C., has stated, "It makes sense to minimize damage by making it mandatory to include a proper portion of groups who will use a drug in studies of that drug.").

77. 58 Fed Reg at 39406 (cited in note 1).
79.

The agency believes that removal of the prohibition on participation of women of childbearing potential in phase 1 and early phase 2 trials is consistent with congressional efforts to prevent unwarranted discrimination against such women. For example, in the employment context, the Pregnancy Discrimination Act, as interpreted by the U.S. Supreme Court in the landmark case of [UAW v Johnson Controls, 499 US 187 (1991)], prohibits the blanket exclusion of pregnant women from jobs they are qualified to perform solely because the working conditions of those jobs pose potential risks to exposed fetuses. The Court emphasized that "decisions about the welfare of future children must be left to the parents who conceive, bear, support, and raise them, rather than to the employers who hire those parents." While the purposes of clinical trials to develop safe and effective drugs are manifestly different from the purposes of private employment, FDA takes serious note of the Court's position on a woman's right to participate in decisions about fetal risk and believes it is appropriate to consider the Court's opinion in developing policy on the inclusion of women in clinical trials.

58 Fed Reg at 39408 (cited in note 1).
81. See notes 64-67 and accompanying text.
conceives, whereas a female subject must provide such informed consent.\textsuperscript{82}

Second, pharmaceutical companies are not likely to be sued for including women in clinical trials. Lawsuits brought by subjects in clinical trials are very rare.\textsuperscript{83} Pharmaceutical companies are particularly concerned about suits brought by children whose parents were subjects. In most states children may bring a lawsuit when they reach age 21 if they are adversely affected by the medical decisions of a parent.\textsuperscript{84} However, if the pharmaceutical company obtains informed consent from the parent, it is unlikely such a suit would succeed.\textsuperscript{85} So, pharmaceutical companies will not increase their exposure to liability by including women.

Unfortunately, pharmaceutical companies are correct in their assessment that they are not likely to be sued for excluding women. Currently, if an injured woman sues a manufacturer for not testing the drug on women, she must prove that the drug should have been tested on women and that the drug caused the injury because it was not tested on women.\textsuperscript{86} Since the injured woman does not have a laboratory and the financial resources to study and prove this causation, her claim will be dismissed for failure to state a cause of action. This Comment therefore proposes shifting the burden of causation so that injured women may succeed in suing pharmaceutical companies. With the shifted burden, the risk of liability will be much higher for excluding women than for including women.

III. Proposed Litigation Model

A. Litigation Goal: Appropriate Inclusion

Fertile women should be included in early phases of drug trials and, in some circumstances, in large numbers in later phases. The pharmaceutical manufacturers are justified in their concern for harm to fetuses; potential injury can, however, be prevented for the most part through the precautions described above, if the precautions are taken for both male and female subjects. The manufacturers are also justified in their concern about greatly increased costs if they are to include every subgroup in large numbers to detect any differences in drug reaction among subgroups. When deciding whether representatives of subgroups must be included, there are scientific, economic, and ethical considerations.

Phase 1 subjects must be demographically representative (e.g. of gender, race, age, etc.) of the targeted market so that they each can have a reasonable impact on the early study. Such a subject pool is only marginally more expensive than

\textsuperscript{82} Merton, \textit{Exclusion of Pregnant, Pregnable, and Once-Pregnable People} at 65 (cited in note 59).
\textsuperscript{83} Merkatz, 329 New Eng J Med at 295 (cited in note 1).
\textsuperscript{84} Id.
\textsuperscript{85} Merton, \textit{Exclusion of Pregnant, Pregnable, and Once-Pregnable People} at 65 (cited in note 59).
\textsuperscript{86} See notes 149-53 and accompanying text.
an all middle-aged white male pool (the additional costs are due to recruiting different kinds of people with different needs). The decision whether to include large numbers of members of any of the subgroups in later phases should be based on the results of the phase 1 study and on any other existing data, such as animal studies, toxicology studies, and available scientific knowledge of the substances in the drug and their effects in humans.\textsuperscript{87} Subgroup, in this context, means any group for which a hypothesis exists that it is biologically plausible for it to be affected differently by the drug being studied. For example, there may be times when women using oral contraceptives or estrogen replacement should be included in large numbers so that differences in responses between them and patients not on such therapy can be examined.\textsuperscript{88}

This Comment's proposed method for determining whom to include during each phase is essentially the same as the system urged in the FDA's new guideline.\textsuperscript{89} Commercial drug manufacturers, however, have not yet used this method of inclusion, and this Comment therefore advocates increasing the likelihood of liability due to exclusion.

B. PRODUCT LIABILITY SUITS\textsuperscript{90}

Although tort law varies by state, I have categorized three kinds of suits that can be adapted to any state's laws: suits alleging failure to provide safe products,

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\textsuperscript{87} For similar recommendations, see Angell, 329 New Eng J Med at 272 (cited in note 33). See also Wenger, Speroff, and Packard, 329 New Eng J Med at 252 (cited in note 54).

\textsuperscript{88} 58 Fed Reg at 39410 (cited in note 1). There is less of a consensus on whether currently pregnant women should be included. The AMA and the FDA plan to explore this issue further and have not released any clear positions as yet. AMA Response at 2 (cited in note 8). One of the arguments for including men and women of reproductive capacity in clinical trials is that precautions can be taken against their conception. Clearly, no precautions against conception are available for pregnant women. However, drugs are often prescribed to pregnant women. See Merkatz, 329 New Eng J Med at 295 (cited in note 1) ("[M]any drugs are ultimately used during pregnancy without reliable data on their maternal and fetal effects."). Some have argued that this is a case where post-marketing data needs to be better collected, rather than collecting data prior to marketing. Id. I disagree; the argument that it is better to test a drug on a few subjects than harm many people on the market applies equally to pregnant women. The solution to this problem is to be even more comprehensive in the informed consent and clinical design protocol when pregnant women are included for the study of drugs for use during pregnancy, but not to exclude pregnant women from studies.

\textsuperscript{89} See 58 Fed Reg at 39406-11 (cited in note 1).

\textsuperscript{90} Other kinds of lawsuits have been proposed. One very promising legal claim is a suit against an institutional review board ("IRB") or the FDA, since these are both in the position of approving test protocols. See Merton, \textit{Exclusion of Pregnant, Pregnable, and Once-Pregnable People} at 88-90 (cited in note 59). An equal protection suit brought against the FDA for its explicit policy of excluding women, which has been proposed, is no longer useful due to the new FDA guideline. See L. Elizabeth Bowles, \textit{The Disfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap}, 45 Vand L Rev 877, 901-07 (1992).
failure to test, or failure to warn. The principles described in all three should be applicable to some extent in each state.

An issue raised in many drug product liability suits is whether FDA approval preempts state tort law. In general, FDA approval of a drug for marketing does not exempt the manufacturer from liability for damage caused by the drug after marketing. The majority of states have held that compliance with FDA standards is insufficient to immunize the drug manufacturer from state tort claims. So, a jury may find that a manufacturer was unreasonably dangerous or negligent even if the drug complied with FDA minimum requirements. Since the goal of both the FDA regulations and state tort law is to provide the consumer with safe and effective pharmaceutical products, most courts view state tort actions as increasing the incentive for drug manufacturers to improve the quality and safety of their products.

The standard of liability in drug product liability suits also varies by state. Most states have adopted Restatement (Second) of Torts Section 402A, requiring strict liability for pharmaceutical products. These states sometimes mitigate this rule by using Comment k, which protects manufacturers from strict liability on the basis that some products are unavoidably unsafe. But many of these states find that Comment k is not always applicable to drug manufacturers because not all drugs are unavoidably unsafe. Other states use a negligence standard.

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91. Abbot v American Cyanamid Co., 844 F2d 1108, 1112-13 (4th Cir 1988) (holding that FDA approval did not preempt Virginia common law liability); Mazur v Merck & Co., 742 F Supp 239, 247 (E D Pa 1990) (holding that compliance with FDA regulation does not absolve the manufacturer of liability); Hurley v Lederle Lab., 851 F2d 1536, 1539-40 (5th Cir 1988) (holding that FDA approval of drug labeling does not preempt state law); Graham v Wyeth Lab., 666 F Supp 1483, 1493 (D Kan 1987) (holding that "[w]hile Congress intends vaccines to be at least as uniformly safe as the FDA regulations require, there has never been a congressional intent that innocent victims of adverse reactions should be precluded from being compensated"); Feldman v Lederle Lab., 97 NJ 429, 479 A2d 374, 391 (1984) (holding that regulation by the FDA will not insulate drug manufacturers from liability under state law).

92. Salmon v Parke, Davis & Co., 520 F2d 1359, 1362 (4th Cir 1975) (holding that compliance with FDA regulations, while pertinent, does not in itself absolve a manufacturer of liability); MacDonald v Ortho Pharmaceutical Corp., 394 Mass 131, 475 NE2d 65, 70-71 (1985) (holding that compliance with the FDA standards was not a shield against state tort liability). But see Grundberg v Upjohn Co., 813 P2d 89, 95 (Utah 1991) (holding that FDA approved prescription drugs are unavoidably dangerous in design, therefore manufacturers are immune from strict liability).

93. Malek v Lederle Lab., 125 Ill App 3d 870, 466 NE2d 1038, 1039-40 (1984) (holding that a jury may consider compliance with FDA regulations in determining reasonableness, but that compliance is not conclusive).

94. Graham, 666 F Supp at 1493. But see Frederick H. Fern and Lewis Bartell, Federal Preemption of Pharmaceutical Labeling, For the Defense 20 (July 1987) ("The courts should defer to FDA's expertise in the field, and give controlling weight to FDA's approval of a drug's labeling.").

95. Restatement (Second) of Torts § 402A (1965); Feldman, 479 A2d at 380.

96. Restatement (Second) of Torts § 402A, Comment k (1965); Feldman, 479 A2d at 381-82; Brown v Sup Ct, 44 Cal3d 1049, 751 P2d 470, 477 (1988).

97. Feldman, 479 A2d at 383; Hill v Searle Lab., 884 F2d 1064, 1068-69 (8th Cir
standard for pharmaceutical products.98

1. Failure to provide safe products.

In those states that have adopted Section 402A, a woman injured by a drug could bring a failure to provide safe products suit against a pharmaceutical manufacturer. These suits create incentives to better design drugs. Especially where the alleged defect is that the drugs are not safe for women, the incentive is to design drugs that are safe or safer for women, and this means better testing.

To achieve this impact, the suit must be brought by a plaintiff, injured because a drug she took was not safe for women, against a manufacturer who could have reasonably prevented the plaintiff's injuries by (1) testing the drug on women, (2) learning through testing that (a) it is impossible to create such a drug that is safe for women, or (b) there is a more effective drug for women or a more effective dosage for women, and/or (3) by labeling the drug accordingly.

A drug manufacturer has a duty to distribute a product that is fit for its intended purpose.99 A seller of any product "in a defective condition unreasonably dangerous to the user or consumer" is subject to liability for physical harm to the user if the seller is engaged in the business of selling the product and the product has reached the user without substantial change in its condition when sold.100 Liability may attach even if the seller exercises "all possible care" in preparation of the product and despite the absence of any contractual connection between the user and the seller.101 The focus is not on whether the manufacturer or seller was at fault, but on whether the product itself was flawed. "[T]he design must be as safe as the best available testing and research permits."102

One rationale for holding manufacturers and sellers of defective products strictly liable without regard to privity, foreseeability, or due care, is that they are able to distribute costs among all of the customers who benefit from the product.103 "Where experiment or research is necessary to determine the presence or the degree of danger, the product must not be tried out on the public, nor must the public be expected to possess the facilities or the technical knowl-
edge to learn for itself of inherent but latent dangers."\textsuperscript{104}

Under a strict liability standard, once the plaintiff proves that the injury was caused by the defect, the manufacturer bears the burden of proving that its actions in marketing the drug were reasonable in light of the expert knowledge in the field.\textsuperscript{105} Also, if the manufacturer's defense is that it could not know of the defect, it bears the burden of proving that it was unable to discover the defect.\textsuperscript{106}

If the state mitigates Section 402A with Comment k, the plaintiff would have to argue that the drug is not unavoidably unsafe because the manufacturer could have avoided the injury either by testing on women or by labeling the drug. The inquiry whether a drug is unavoidably unsafe is essentially the same as whether a manufacturer was negligent.\textsuperscript{107} Discussions of two kinds of negligence suits follow.

2. Failure to test.

Drug companies have been found liable for inadequate research.\textsuperscript{108} This principle can be extended and applied to failure to conduct research on women, including fertile women and even pregnant women, that would have revealed the specific risks which ultimately appeared in the female population when the drug was approved and sold. The incentive created by failure to test suits is better tests. Particularly where the alleged failure is the failure to test women subjects, the suit creates an incentive to test drugs on women.

The suit requires a plaintiff to claim that her injuries were caused by a drug she took that was not tested on women.\textsuperscript{109} Had the drug been so tested, the manufacturer would have known of its side-effects, and therefore the manufacturer would have warned the patient's physician of the possible or likely injury to her as a woman taking the drug, and with that warning she would not have taken the drug.

When the defect consists of an improper design, the reasonableness of the manufacturer in marketing the product is a factor in determining liability.\textsuperscript{110} "A manufacturer's duty of reasonable care includes a duty of product inspection and testing . . . as is reasonably necessary to render the product safe for its users."\textsuperscript{111} If the drug in the suit is one which the manufacturer foresaw would be sold to women, the manufacturer should have considered the effects of the drug on women. Based on toxicology studies and other scientific data, the manufacturer should have decided whether it needed to include large numbers of women

\textsuperscript{104} Dalehite v United States, 346 US 15, 52 (1953) (Jackson dissenting).
\textsuperscript{105} Feldman, 479 A2d at 385.
\textsuperscript{106} Id at 388.
\textsuperscript{107} Graham, 666 F Supp at 1498; Feldman, 479 A2d at 385-86.
\textsuperscript{108} See, for example, Taylor v Wyeth Lab., 139 Mich App 389, 362 NW2d 293, 296 (1984).
\textsuperscript{110} Id; Feldman, 479 A2d at 385-86.
\textsuperscript{111} Taylor, 362 NW2d at 296.
or a particular subgroup of women in its clinical trials.\textsuperscript{112} Any drug that will be sold to women should include women in its phase 1 trials, or else the manufacturer will not know whether or not the drug will hurt women.\textsuperscript{113} Liability may attach when the manufacturer knew of the defect in the product and did not act in a reasonably prudent manner in marketing the product.\textsuperscript{114} This principle can be applied where the defect is that the drug was not tested on women and the drug is then marketed to both men and women.

The duty to test is supported by federal law and FDA regulations that require a New Drug Application ("NDA") to demonstrate "adequate and well-controlled investigations, including clinical investigations ..."\textsuperscript{115} and to include "data demonstrating substantial evidence of effectiveness for the claimed indications."\textsuperscript{116} The court in Toole \textit{v} Richardson used Section 355(b) of the Federal Food, Drug, and Cosmetic Act to hold that the adequacy of tests of MER/29 "is strictly for the determination of the [FDA]."\textsuperscript{117} The defendant was found liable for failing to pursue abnormalities in test animals.\textsuperscript{118}

The FDA regulations further state that "[e]vidence is also required to support the dosage and administration section of the labeling ... and modifications for specific subgroups (for example, pediatrics, geriatrics, [and] patients with renal failure)."\textsuperscript{119} "If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease ... the labeling shall describe the available evidence and state the limitations of usefulness of the drug."\textsuperscript{120}

In interpreting what adequate testing means under these statutes, the courts assume that pharmaceutical companies have all the information of experts in the field.\textsuperscript{121} Manufacturers are under a duty to keep abreast of current developments, and knowledge of such developments is imputed to them.\textsuperscript{122} There is a scientific consensus on gender-related differences both in effectiveness of drugs and side-effects of drugs. The FDA and AMA have both released statements acknowledging that these differences exist and must be pursued in clinical tests.\textsuperscript{123} The leading national medical journals have published articles with
similar conclusions.\textsuperscript{124} Passages from the FDA guideline demonstrate the clear, expected standard.\textsuperscript{125} Therefore, the experts are in agreement that it is not unavoidable that a drug was not tested on women. Clearly, the PMA has read the FDA guideline, which explicitly states what is appropriate.\textsuperscript{126} No pharmaceutical company can successfully claim that it does not know about the new FDA guideline or the consensus in the field.

Courts have engaged in quite close scrutiny of the research design of clinical trials and criticized them for their lack of relevance to actual market conditions.\textsuperscript{127} In general, “[t]esting procedures should simulate as closely as possible the anticipated conditions of marketing and use of the product.”\textsuperscript{128} If a product is intended for long-term use, testing it in short-term trials which fail to detect a side effect may subject a manufacturer to liability.\textsuperscript{129}

This Comment has discussed how a pharmaceutical company should decide how many women must be included in clinical trials.\textsuperscript{130} Similarly, “[t]he [FDA] guidelines urge that reasonable numbers of women be included in studies of new drugs. ‘Reasonable numbers’ are not defined precisely; rather, the agency expects enough representation of both sexes so that significant differences can be detected.”\textsuperscript{131}

Indications of a disparate occurrence of an adverse effect in one particular subpopulation of foreseeable users has been held sufficient to trigger an obligation to conduct further research “reasonably necessary to render the product safe for its users.”\textsuperscript{132} Courts penalize companies that do not conduct reasonable testing to determine the potential adverse reactions of their products, even if the testing involved was not required by the FDA.\textsuperscript{133} The reason most courts give

\textsuperscript{124} See, for example, Cotton, 267 JAMA at 469-73 (cited in note 43); Bennett, 329 New Eng J Med at 288-91 (cited in note 9); Pinn, 268 JAMA at 1921-22 (cited in note 53).
\textsuperscript{125} See, for example, 58 Fed Reg at 39410-11 (cited in note 1).
\textsuperscript{126} The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response. . . . [I]t is prudent to at least carry out pilot studies to look for major pharmacokinetic differences before conducting definitive controlled trials, so that differences that might lead to the need for different dosing regimens can be detected.
\textsuperscript{127} Tinnerholm v Parke Davis, 285 F Supp 432, 446-48 (S D NY 1968), modified and aff'd, 411 F2d 48 (2d Cir 1969) (upholding negligence claim of child injured by vaccine that was "rush[ed] to commercialization" without testing under market conditions).
\textsuperscript{128} Marden G. Dixon and Frank Woodside, Drug Product Liability, § 14.04(2) at 14-68 (M. Bender, 1990).
\textsuperscript{130} See text accompanying notes 87-89.
\textsuperscript{131} Merkatz, 329 New Eng J Med at 294 (cited in note 1).
\textsuperscript{132} Taylor, 362 NW2d at 296-97.
\textsuperscript{133} Barson, 682 P2d at 836 (manufacturer negligent for not testing for teratogenic effects of injected progestational hormone); West v Johnson & Johnson Products, Inc., 174
for not holding that FDA regulations preempt state law is that the FDA regulations are a minimum requirement. Here, there is an FDA guideline expressing, though not requiring, the standard for including women in clinical trials. So, it would be easy for a state court to find that its tort laws require the manufacturer to meet that standard.

Product liability law generally imposes a duty on a manufacturer to directly warn foreseeable users of any known dangers associated with the use of a product.134 However, in most jurisdictions, a manufacturer of prescription drugs can discharge this duty either by warning the consumer directly, or by warning a "learned intermediary," traditionally the treating or prescribing physician.135

Of the relatively few tort complaints that have attempted to hold drug companies responsible for harm on a theory of insufficient research, most focus their pleadings on the manufacturer's failure to warn of risks that it would have known about, had proper clinical research been conducted, rather than on a failure to test per se. That is, the manufacturer lacks information that could and should have been transmitted to the consumer, or with prescription drugs, to the prescribing physician, because it failed to conduct the research that would have developed that information.

3. Failure to warn.

Drug companies have been found liable for not warning consumers of a danger of a drug.136 This principle can be extended and applied to failure to warn that no research was conducted on the effects of a drug in women.

The incentive created by failure to warn suits is better labeling for the consumer or greater notice of the extent of clinical testing to doctors. The impact of this suit, therefore, is not as great as the above two kinds of suits which might lead directly to improved testing. Labels (or notice to doctors) indicating that a drug was not tested on women, or not tested on women with reproductive capacity, would not make the drug any safer for women who will most likely need to take the drug regardless of this label (or notice). Labels could, however, have a political impact if they caused large numbers of women to become aware that drugs are not being tested on them. Notice to doctors could have an impact if doctors became frustrated by repetitive off-label prescriptions. Also, labels could have an impact if some drug companies test on women and their drugs' labels state that they are safe for women, and other drugs' labels say they have not been tested on women. Then, the companies that test on women will benefit

134. Frederick H. Fern, The Decline and Fall of the Learned Intermediary Doctrine, For the Defense 10 (Sept 1986).
135. Id.
136. See, for example, Barson v E.R. Squibb & Sons, Inc., 682 P2d 832, 835 (Utah 1984) (failure to warn of a known danger is negligent per se).
A failure to warn suit requires a plaintiff who was injured because a drug she took did not have a label indicating it was not tested on women (or her doctor was given no notice). The plaintiff must further be able to show that, had there been such a label (or notice), she would not have taken the drug. The legal claim is that such a label is reasonable and it is foreseeable that the lack of warning would have this effect.

"[L]iability may attach if the manufacturer [did] not take available and reasonable steps to lessen or eliminate the danger of even a significantly useful and desirable product."

When the risk is not apparent, consumers must be warned of concealed dangers in an adequate and comprehensible way. As stated above, with pharmaceutical products, the manufacturer's duty to warn may be discharged by warnings to the physician or to the patient. Failure to warn of known dangers may be considered either negligence or a kind of defect in the product marketed. If the injured party can also prove that the warning would have prevented the injury and thus that the failure to warn caused the injury, damages may be recoverable from the seller of the product.

The manufacturer's failure to warn of a danger in a drug that the manufacturer knew or should have known about subjects the manufacturer to liability. In Barson v E.R. Squibb & Sons, Inc. the court held that failure to warn of a known danger is negligent per se and subjects the manufacturer to direct liability whether knowledge was constructive or actual.

The standard for adequate warnings is based in both common law and federal regulation. The warnings must be accurate in content and conveyed through an appropriate means and style of communication. The duty to warn is limited to those risks which were reasonably foreseeable at the time the drug was prescribed and used. If the seller realizes, however, that its knowledge of potential adverse effects is limited, it should at least warn the consumer that the product is experimental and may present unknown hazards.

A drug package insert represents an agreement between the manufacturer and the FDA. Many drugs are not tested on enough of a certain population, so the insert says, "Not recommended for such and such population" or "Not tested on

138. Brochu, 642 F2d at 656.
140. Ezagui v Dow Chemical Corp., 598 F2d 727, 736 (2d Cir 1979).
142. Barson, 682 P2d at 835.
143. Sterling Drug Inc. v Yarrow, 408 F2d 978, 992 (8th Cir 1969) (unreasonable to fail to instruct "detail men" who regularly saw prescribing physicians to warn the physicians about drug risks).
such and such population.”

Doctors are liable when they prescribe “off-label” unless they give sufficient warning to the patient.

For the plaintiff, the hardest part of the failure to warn suit is proving causation. To be liable for a failure to warn, the injured individual must show that she would not have used the drug had a proper warning been given.

C. PROVING CAUSATION (AVOIDING A NONSUIT FOR LACK OF INFORMATION ON CAUSATION)

For the above tort suits, the plaintiff may have difficulty proving the causal link between the drug and the event necessary for legal action. While the manufacturer has the resources and the interest to conduct research on its product, a plaintiff is unlikely to have the resources to hire an expert to conduct research on the product. The company is unlikely to invest in epidemiological or controlled studies that may reveal a genuine systematic problem if it believes it can instead dismiss whatever evidence emerges on the market as “anecdotal” or “meaningless coincidental clusters.” This creates somewhat of a Catch-22 situation. If the manufacturer does not test on women, there is no evidence that the manufacturer should have tested on women because there is no evidence of how the drug reacts in women.

1. Traditional procedural steps for proving causation.

There are two levels of proof for causation in toxic tort suits: general causation and specific causation. To prove general causation the plaintiff must show that the drug in question is capable of causing the alleged injury. This proof may consist of animal studies (where animals are given huge doses of the drug) or toxicology studies (that look at whether the active ingredients in the drug, not the inert ingredients, could cause the effect or injury).

Recently, the Supreme Court in Daubert v Merrell Dow Pharmaceuticals, Inc. rejected the requirement that scientific evidence be generally accepted as valid in the scientific community before being admissible in court. In effect, this holding removed the requirement of epidemiological proof. Epidemiological studies involve a large number of humans and statistical analyses; they are very expensive. The Court in Daubert stated that, instead, admissible proof may consist of a hypothe-

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146. Telephone Interview with Joseph W. Cranston, M.D., Director of the Department of Drugs at the AMA (Nov 1993) (There are many off-label uses, including 80% of pediatric prescriptions and 50% of cancer prescriptions.).

147. Id.


151. Telephone Interview with researchers at multiple laboratories in Chicago, Illinois (Nov 1993).
sis of causation made by the scientific community.\textsuperscript{152}

To prove specific causation, the plaintiff must show that the drug in fact caused the plaintiff's injury and that the defendant pharmaceutical company in fact made the drug taken by the plaintiff. The plaintiff must also demonstrate, through adequate studies, a relationship between the exposure and her injuries. Courts can and should scrutinize these studies, making the burden of proof difficult to meet.\textsuperscript{153}

For the kinds of drug product liability suits discussed in this Comment, general causation is likely to be hard to prove due to the Catch-22 situation described above. The standard of proof may vary by state and by legal claim. For example, a Michigan court held, "[T]his issue is one for the jury, provided there is evidence from which reasonable persons could draw a 'fair inference' that the injury was caused by the negligent omission."\textsuperscript{154}

Possibly, a plaintiff could succeed in proving causation by hiring an expert witness to run a study or to state an obvious hypothesis that women should have been studied (based on existing animal studies, toxicology studies, or other existing scientific knowledge). But there might be a statute of limitations problem with the expert conducting a study because studies can take a long time, and the study might be too expensive for plaintiff's counsel.

It is unreasonable for the legal system to expect a plaintiff to hire an expert to run a study when the defendant manufacturer is obviously the party responsible for doing so in the first place. It is reasonable for the legal system to expect a plaintiff to hire an expert to dispute the manufacturer's choice not to study large numbers of women or a subgroup of women. For example, in \textit{West v Johnson & Johnson Products, Inc.} the plaintiff's experts asserted "(1) that adequate testing would have revealed an association between tampon use and vaginal infection, and ultimately between such use and menstrually-related TSS [toxic shock syndrome]; (2) that JJP's [Johnson & Johnson's] testing was inadequate; (3) that JJP's decision not to do any further testing... was a conscious one; and (4) therefore, JJP acted in conscious disregard of the safety of others."\textsuperscript{155} The California Court of Appeals for the Sixth District upheld the jury decision that the defendant was negligent.\textsuperscript{156}

\textsuperscript{152} \textit{Daubert}, 113 S Ct at 2794.
\textsuperscript{154} \textit{Taylor v Wyeth Lab.}, 139 Mich App 389, 362 NW2d 293, 297 (1984) (holding that medical research articles submitted into evidence by plaintiff were sufficient evidence of what the results of tests might have been).
\textsuperscript{155} \textit{West v Johnson & Johnson Products, Inc.}, 174 Cal App 3d 831, 220 Cal Rptr 437, 460 (1985).
\textsuperscript{156} Id.
2. Tort law reform: shift the burden of production and create a rebuttable presumption that defendants' lack of testing is the cause.

In order to provide the proper incentives to manufacturers and to be fair to plaintiffs, courts may need to shift the burden of production on the issue of general causation and create a rebuttable presumption that the defendant's lack of testing is the cause of the injury. In all states besides California, this may require a statute passed by the legislature. In California, the courts have allowed such burden shiftings and presumptions without legislative statutes.157

a) Legal rationale for shifting the burden. In Haft v Lone Palm Hotel the California Supreme Court held that the plaintiffs met the initial burden of proof on the issue of causation by showing that the defendants violated a statute requiring either a lifeguard at their pool or a sign indicating that there is no lifeguard.158 The burden then shifted to the defendants to show that this violation was not a proximate cause of the deaths.159 If the defendants could not prove the violation was not the proximate cause, then causation would be presumed.160

Similarly, a woman could show that a pharmaceutical manufacturer did not test on women, which violates the FDA regulation of adequate testing for all NDAs.161 The burden would then shift to the manufacturer to show that this violation was not a proximate cause of the injury the woman suffered. If the manufacturer failed to show that its refusal to test on women was not the proximate cause of her injury, the manufacturer's inadequate testing would be the presumed cause. To rebut the presumption, the manufacturer could argue that it would not have been reasonable to test on women, or that it is scientifically impossible for the drug to cause the injury the plaintiff has suffered.

The Haft court's decision to shift the burden was based on the difficulty the plaintiff faced in attempting to show causation.162 The court held that where

157. See, for example, Haft v Lone Palm Hotel, 3 Cal 3d 756, 478 P2d 465, 470 (1970) (en banc).
158. Haft, 478 P2d at 470.
159. Id.
160. Id at 473.
161. See text accompanying notes 115-20.
162. The troublesome problems concerning the causation issue in the instant case of course arise out of the total lack of direct evidence as to the precise manner in which the drownings occurred. Although the paucity of evidence on causation is normally one of the burdens that must be shouldered by a plaintiff in proving his case, the evidentiary void in the instant action results primarily from defendants' failure to provide a lifeguard to observe occurrences within the pool area. . . . The absence of such a lifeguard . . . not only . . . [increased plaintiffs' risk of harm], but also deprived the present plaintiffs of a means of definitively establishing the facts leading to the drownings. Clearly, the failure to provide a lifeguard greatly enhanced the chances of the occurrence of the instant drownings. . . . [P]laintiffs have gone as far as they possibly can under the circumstances in proving the requisite causal link between defendants' negligence and the accidents. To require
the defendant's negligence makes it impossible, as a practical matter, for the plaintiff to prove "proximate causation" conclusively, it is more appropriate to hold the defendant liable than to deny an innocent plaintiff recovery, unless the defendant can prove that his negligence was not a cause of the injury.163

Similarly, in Summers v Tice, the court held that the impossibility of the plaintiff's task in determining which of two defendants had caused his injury required the burden of proof to shift to the defendants as a matter of fairness and in view of the parties' relative fault.164 The court stated that the practical difficulties facing the plaintiff bore considerable similarity to the problems the court addressed earlier in Ybarra v Spangard.165

In Ybarra the plaintiff confronted the formidable task of proving which of the doctors and attendants who participated in his operation while he was unconscious were responsible for his injury. The court held that under the doctrine of res ipsa loquitur, the plaintiff could maintain his claim against all the persons who had a connection with the operation, and the burden was placed on the individual defendants to demonstrate their non-involvement.166 “[The] plaintiff has made out a case when he has produced evidence which gives rise to an inference of negligence which was the proximate cause of the injury. It is up to the defendants to explain the cause of the injury.”167

An injured female plaintiff brought a suit in 1985 which argued for such a shift in the burden and for such a presumption.168 The plaintiff in Jones v Ortho tried to hold the manufacturer liable for its failure to conduct clinical trials that could have established whether its product contributed to her cancer. Her legal theory relied on a since-revised section of FDA regulations that stated that new drug applications must provide "adequate information" consisting of reports of "an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug..."169 Her argument was that the company's failure to investigate this potential risk made it impossible for her to establish the causal link that would sustain her underlying claim for the cancer, and that therefore the burden to demonstrate the causal connection between the drug and her cancer should be

plaintiffs to establish 'proximate causation' to a greater certainty than they have... would permit defendants to gain the advantage of the lack of proof inherent in the lifeguardless situation which they have created. Under these circumstances the burden of proof on the issue of causation should be shifted to defendants to absolve themselves if they can.

Haft, 478 P2d at 474-75 (citations omitted).
163. Id at 476.
164. Summers v Tice, 33 Cal 2d 80, 199 P2d 1, 4 (1948) (en banc).
166. Ybarra, 154 P2d at 689-90.
167. Summers, 199 P2d at 4 (discussing Ybarra).
169. Id at 462 n 5.
considered presumptively met, subject to rebuttal from the company. The California Court of Appeal granted a nonsuit for failure to show causation. The court may have been unlikely to grant the plaintiff's theory because even her own expert witnesses could not say that it was likely that her cancer was caused by the drug and could only say that it might be possible. Also, the court suggested that the plaintiff's sexual activity at an early age, with multiple partners, and the presence of venereal warts contributed to the cancer. A court might accept the plaintiff's theory with either a stronger expert witness, stronger scientific probabilities, or with a plaintiff that the court found sympathetic. Her legal theory is quite logical.

A rebuttable presumption that the defendant's lack of testing caused the injury to the woman would allow the complaint to survive longer in the litigation process. The complaint would not be dismissed early for failure to state a claim. The rebuttable presumption requires defendants to take the suit more seriously. Even if the case is settled rather than tried in court, the defendant pharmaceutical company will know that the reason it is paying damages is because it failed to test on women when it should have.

b) Policy rationale for shifting the burden. The Haft court stated that major factors to consider in deciding whether to shift the burden of proof on the issue of causation are the relative culpability of the parties and the burden facing the plaintiffs in providing the information. Relative culpability of the parties includes the innocence of each as well as the ability to prevent the harm. The burden facing the plaintiffs involves the resources available to discover the information and their access to the information.

The first major factor in considering whether to shift the burden is the relative culpability of the parties. The culpability of the injured plaintiff must be determined in evaluating the relative culpability of the parties. In Sindell v Abbott Laboratories, the California Supreme Court applied the theory that the burden of proof of causation is placed upon tortious defendants in certain circumstances. The court stated that the reasoning behind Summers may be extended.

170. Id at 461.
171. Id.
172. Id.
173. Id at 460.
174. Haft, 478 P2d at 476.
175. [A]s between an innocent plaintiff and negligent defendants, the latter should bear the cost of the injury. Here, as in Summers, plaintiff is not at fault in failing to provide evidence of causation, and although the absence of such evidence is not attributable to the defendants either, their conduct in marketing a drug the effects of which are delayed for many years played a significant role in creating the unavailability of proof. From a broader policy standpoint, defendants are better able to bear the cost of injury resulting from the manufacture of a defective product.

The relative culpability of the parties is even stronger in a failure to test drug product liability suit. Although the plaintiff would be as innocent as the plaintiffs in *Sindell*, the defendant manufacturer is more clearly culpable (assuming there are no problems in proving specific causation). The defendant manufacturer is required to adequately test under FDA regulations, and the manufacturer is negligent if no tests on women are conducted in violation of the medical industry standard described above.

The culpability of the defendant pharmaceutical corporation is also a factor in evaluating the relative culpability of the parties. In a failure to test drug liability case, the plaintiff's difficulty in showing causation is due to the lack of medical research on how the drug behaves in women. This lack of medical research is due precisely to the alleged violation by the defendant. Clearly, the failure to test on women greatly enhances the chances of an injury to a woman who uses the drug. To require the woman to prove the causal medical link between the lack of testing and the injury would be to give pharmaceutical companies the message that they can avoid testing on women because there will be no way for an injured woman to sue successfully. In a drug product liability failure to test suit, the defendant manufacturer also exercises control over its clinical trials, creates the dangerous condition, and profits from the manufacture of the drug.

Determining which party is best able to prevent the harm is also important in determining the relative culpability of the parties. Since the defendant drug company is the one to decide whether or not to test women subjects, the defendant is in the best position to prevent the harm that occurs when a drug injures a woman when that drug was never tested on women.

The *Summers* court described the policy behind shifting the burden of proving causation to defendants and imposing alternative joint liability: "The injured party has been placed by defendants in the unfair position of pointing to which defendant caused the harm. . . . Ordinarily defendants are in a far better position to offer evidence to determine which one caused the injury." The reason underlying the *Summers* rule is "the injustice of permitting proved wrongdoers . . . to escape liability merely because the nature of their conduct and the resulting harm has made it difficult to prove which of them has caused the harm." The *Haft* court said that its facts presented "a stronger case for shifting the

176. For the same reasoning, see *Haft*, 478 P2d at 477.

If the pool owner can disregard the statute and retreat to the sanctuary of the argument that the plaintiff must prove the 'cause' of the death which obviously is unknown, he can, without liability, expose his paying patron to the very danger that the statute would avoid. Since the pool owner violates the statute, since he creates the dangerous condition and exercises control over it, since the death occurs upon his premises with which he is familiar, since he profits from the presence of the pool, he cannot take refuge in the position that the burden of proof rests with the probable victim of his statutory violation.


178. Restatement (Second) of Torts § 433B, Comment f (1965).
burden of proof to defendants than *Summers*, because [the *Haft* defendants] are in a sense more 'culpably' responsible... than were the [defendants] in *Summers*.'

In a failure to test drug product liability case, the pharmaceutical manufacturer defendant is at least as culpable as the defendants in *Summers* and *Haft*.

The second major factor in considering whether to shift the burden is the burden facing the parties in providing the information. One way to determine the difficulty in providing the information is to consider the resources available to discover the information.

One tort law scholar has argued that the burden of proof on causation should be shifted to the defendant in all drug tort cases because of the power imbalance between the parties. She points out that in criminal cases the government, a large and powerful party, is against an individual and that the justice system has therefore attempted to heavily weight presumptions in favor of the individual defendant. She argues by analogy that in drug tort cases there should be presumptions in favor of the individual injured plaintiff over the large manufacturing corporation.

The justice system should not expect an injured individual to undertake the kind of epidemiological or clinical research that is required to meet the heavy burden of proving the element, necessary to any recovery, of causation. Drug manufacturers will almost always be in a far better position to research the issue, at least in the negative sense of proving that no or few adverse experience reports attributing a similar problem to the drug have been submitted.

Another way to determine the difficulty in providing the information is to consider the access to the information. To prove the element of causation a plaintiff must present some evidence, on which an expert witness could base an opinion, revealing the potential for a different reaction of the drug in women generally or in some women. Although there is increasing scientific knowledge of differences in the way men and women react to drugs, acquiring this information with regard to a particular drug may be hard. Jean Hamilton, M.D., Director of the Institute for Research on Women's Health in Washington D.C., has stated that differences are not seen "unless we stumble upon them, and what we've stumbled upon so far is the tip of the iceberg." In other words, a drug may very well cause adverse effects only in women, but there may be little evidence of this if the manufacturer included no or few women in its studies. Therefore, if the legal system is concerned with injury to innocent individuals, it should place the burden (of producing conclusive scientific information on why women did not need to be tested) on the defendant. If the defendants are not at fault, they should have already made this determination and have records of their

179. *Haft*, 478 P2d at 476.
181. Id at 879-80.
182. Id at 880.
183. *Extrapolation* at 1050 (cited in note 1).
decision not to include women at all or in large numbers. Presenting this information should be a relatively easy burden for truly innocent defendant manufacturers.

Similarly, in some recent employment discrimination cases, the Supreme Court has decided that the burden of proof must shift to defendants on the issue of causation. In Justice O'Connor's concurring opinion in *Price Waterhouse v Hopkins* she argued that the burden of persuasion should shift to the employer "where the employer has created uncertainty as to causation by knowingly giving substantial weight to an impermissible criterion." "Presumptions shifting the burden of proof are often created to reflect judicial evaluations of probabilities and to conform with a party's superior access to the proof."

The third major factor to consider in whether to shift the burden of proof on causation is the foreseeability of the result of inadequate testing. The *Sindell* court stated that the standard for shifting the burden of proof to the defendant is whether the absence of evidence of causation is a "direct and foreseeable result" of the defendant's violation. In the failure to test drug product liability suit, the absence of evidence of the causal link between not testing on women and the injury to a woman is the direct and foreseeable result of not testing on women and providing the corresponding test results. "The manufacturer is in the best position to discover and guard against defects in its products and to warn of harmful effects; thus, holding it liable for defects and failure to warn of harmful effects will provide an incentive to product safety. These considerations are particularly significant where medication is involved, for the consumer is virtually helpless to protect himself from serious, sometimes permanent, sometimes fatal, injuries caused by deleterious drugs."

IV. Litigation as a Behavioral Modifier

Litigation has effectively modified the behavior of an industry in the past, and will be effective in modifying the pharmaceutical industry's testing procedures. Another reason for promoting litigation is that nothing else has worked. Recent scientific evidence and governmental policies have been ineffective in encouraging manufacturers to change their testing procedures.

As of 1991, many drug companies believed that the FDA explicitly required that women *not* be included in clinical trials. In November 1993 the FDA
published a new guideline, which emphasizes that "substantial representation of both sexes is expected in studies of safety and effectiveness, and the data should be examined for sex differences in the effectiveness, adverse-event rates, and dose response of drugs. If these analyses suggest differences between the sexes, or if the presence of such differences could be especially important, as in the case of drugs with a low therapeutic index, additional formal studies may be needed."\(^1\)

Will this new guideline affect the practices of the pharmaceutical industry? It is hard to be anything but pessimistic given the response to past nonbinding guidelines issued by the FDA.\(^1\) Indeed, the FDA has stated that it doubts its own guideline will have much effect.\(^1\)

To ensure that it legally need not meet the FDA's expectations, the PMA, in its comments on the new guideline, emphasized that the guideline was not a mandate and that discretion for whether to include women is actually up to the researcher.\(^1\) So, while the FDA guideline and notice have nicely summarized the state of scientific knowledge and have stated a system that is reasonable with regard to including fertile women in clinical trials, the PMA is unlikely to follow the guideline's recommendations.

The PMA's comments on the guideline also demonstrate that its members intend to exclude fertile women. Instead, they plan to actively recruit postmenopausal and surgically sterilized women to fulfill political pressures to include female subjects in trials.\(^1\) These comments suggest that the drug companies prefer a state of inertia to improvement. Although it is definitely better to include post-menopausal and surgically sterilized women than no women, it is best to include women with hormones that are more representative of most women, particularly where one of the major differences in men's and women's responses to drugs has been based on women's menstrual cycle. The PMA's comments on a specific section of the new FDA guideline are a further example of its continued feigned ignorance of scientific knowledge of women's and men's different

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191. For example, in 1988 the FDA "specifically called for studies of whether safety and effectiveness were similar within population subgroups defined by such characteristics as sex, age, and race. Recent evaluations have shown that the requested analyses were not being carried out regularly." Id. FDA representatives have announced that, "[I]n light of these findings, the FDA will review all new drug applications shortly after submission to ensure that they include appropriate analyses by sex. If such analyses are lacking, the FDA will call for their submission and may consider refusing to initiate review of the application if sex-specific analyses are not provided within a reasonable period." Id (citations omitted).
192. 58 Fed Reg at 39408 (cited in note 1) ("The agency recognizes that this change in FDA's policy will not, by itself, cause drug companies or IRB's to alter restrictions they might impose on the participation of women of childbearing potential."). See also id at 39409 ("This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.").
193. PMA Response at 1-2 (cited in note 38).
194. See notes 45-46 and accompanying text.
reactions to drugs. Thus, while the PMA appears to be fighting hard to stay put, the FDA is “confident that the interplay of ethical, social, medical, legal and political forces will allow greater participation of women in the early stages of clinical trials.”

What are these ethical, social, medical, legal, and political forces, and will they lead to change? For one, women are moving into the upper levels of academic medicine. "If women are the teachers of the next generation of doctors and the senior investigators in the next generation of clinical research, women's health will finally get the attention it deserves without the need for special rules.”

Although National Institutes of Health (“NIH”) funding does not directly impact a pharmaceutical company's research, a change in NIH research policies could affect medical research standards. President Clinton signed into law in June 1993 the NIH Revitalization Act, which included a provision that the NIH ensure that all federally funded clinical research include a valid analysis to determine whether the intervention under study affects women or members of minority groups differently from other subgroups. Section 429B of the Act

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195. The relevant section of the FDA guideline states:

Three pharmacokinetic issues related specifically to women that should be considered during drug development are: (1) The influence of menstrual status on the drug's pharmacokinetics, including both comparisons of premenopausal and postmenopausal patients and examination of within-cycle changes; (2) the influence of concomitant supplementary estrogen treatment or systemic contraceptives (oral contraceptives, long-acting progesterone) on the drug's pharmacokinetics; and (3) the influence of the drug on the pharmacokinetics of oral contraceptives. Which of these influences should be studied in a given case would depend on the drug's excretion, metabolism, and other pharmacokinetic properties, and on the steepness of the dose-response curve.

58 Fed Reg at 39411 (cited in note 1). The PMA's response to this section stated, “Of concern . . . is the emphasis given to the influence of menstrual status on drug pharmacokinetics. With no available evidence of changes in drug pharmacokinetics/pharmacodynamics over the menstrual cycle, and the influence of menstrual status on disease states being poorly understood, there seems to be little justification for giving this issue the same emphasis as other drug/hormone interactions during drug development.” PMA Response at 3 (cited in note 38). The PMA, however, needed to read only one paragraph of the guideline further for the evidence it claimed it never heard of. The FDA guideline states, “[h]ormonal status during the menstrual cycle may affect plasma volume and the volume of distribution (and thus clearance) of drugs.” 58 Fed Reg at 39411 (cited in note 1). In addition, plenty of scientific evidence exists in medical journals that describe how response to drugs or other therapeutic interventions varies across the menstrual cycle. “For example, some studies suggest that survival is significantly shorter when breast cancer surgery is performed between the third and 13th days of the menstrual cycle.” Cotton, 267 JAMA at 470 (cited in note 43). Other studies demonstrate that there are menstrual variations in a variety of neurochemical systems and in patterns of drug metabolism and responsiveness. Hamilton and Parry, 38 J Am Med Women's Assn at 127-28 (cited in note 47).

196. 58 Fed Reg at 39408-09 (cited in note 1).
198. Id.
provides that the director of NIH shall ensure that women and members of minority groups are included as subjects in each research project. This requirement does not apply if their inclusion is inappropriate with respect to their health, the purpose of the research, or other circumstances that the director of NIH may designate. This Act, however, is unlikely to have much effect since the NIH has a history of evading policies in this area, and the last exception may swallow the rule, depending on how "appropriate" is defined, who defines it, and when they get around to defining it. Thus, despite the increasing scientific evidence and governmental policies, pharmaceutical companies continue to exclude women.

A. LITIGATION SUCCESS STORIES

Litigation has a successful track record in effecting change. A great deal of literature, including reports by the American Law Institute and by RAND, on the success of tort product liability suits demonstrates that litigation can be very effective in "identifying important new injury problems that warrant social concern" in areas where there is little or no regulation. Interestingly, "many of the most visible and costly product liability episodes in pharmaceuticals . . . include various vaccines, contraceptives, and products to prevent miscarriage and treat morning sickness." Although the RAND Report does not indicate why these suits were particularly effective, many of them involve women-specific drugs. There are two ways companies can respond to potential product liability costs within the product development process: altering the physical characteristics of products to make them safer than required for FDA approval and testing them more thoroughly, If FDA regulations are not strict, it is more likely that product liability will affect change in company decision making and lead to design improvements or greater testing. As discussed above, the new FDA regulation on testing is a recommendation and not a mandatory guideline.

Another success story is that of a single vaccine for diphtheria, tetanus, whooping cough, and polio. The four antigens in the vaccine had each been

200. Id.
201. Id.
202. See Merton, Exclusion of Pregnant, Pregnable, and Once-Pregnable People at 95-102 (cited in note 59).
204. Id. See also Steven Garber, Product Liability and the Economics of Pharmaceuticals and Medical Devices 131 (RAND, 1993).
205. Id at 61.
206. Id at 128.
207. Id at 131.
tested separately, but never tested combined. The vaccine was marketed as an efficient way to vaccinate against all four at once. The pharmaceutical manufacturer who developed, tested, and sold the vaccine never tested it under market conditions. An injured person sued and won, and vaccines have since been tested under market conditions. Thus, in certain circumstances, litigation is likely to be more effective than regulation.

This Comment advocates the adoption of a presumption (either by state legislatures or by state courts) that defendant manufacturers who did not test on women are liable unless they can prove they did not need to test on women. This presumption, and its corresponding burden shift, will allow women who bring these suits to be successful, and will thereby change the behavior of pharmaceutical manufacturers who currently believe the likelihood of a successful suit is low. The RAND Report indicates that companies make decisions based on the likelihood of various outcomes; if companies know that shifting the burden of proof is possible or likely, they may behave differently. The mere threat of litigation may induce researchers to test their drugs on the same population to whom they market their drugs.

209. Id at 446-47.
210. Id at 446.
211. Id.
213. “There is often a considerable lag between the creation of risks by enterprises, the widespread recognition of such risks and the need to deal with them, and the adoption of regulations to control them for the future. Considerable harm may occur in the interim.” American Law Institute, 2 Enterprise Responsibility for Personal Injury: Volume II: Approaches to Legal and Institutional Change 85 (ALI, 1991). “Regulations may also underestimate risks or means for controlling them, judgments that enterprises are often in a better position to make. Liability addresses these shortcomings by giving firms incentives to control risks before regulations are adopted to deal with them.” Id. While regulations tend to be uniform and ignore relevant differences in the activities of firms, “[t]ort liability can fine tune the legal controls on risky behavior.” Id. “Regulatory agency ‘failure’ may occur because of inadequate resources or on account of political and bureaucratic pressures. A system of privately initiated tort remedies, administered through the decentralized, general purpose court system, can serve as a corrective for these shortcomings.” Id at 86. Tort liability also “provides a compensation function not generally performed by regulation.” Id.
214. It is extremely unlikely that Congress would pass an enactment requiring the inclusion of women when phase 1 studies necessitate their inclusion. Congress just passed the NIH Revitalization Act in 1993 after over five years of lobbying. As described above, the NIH Revitalization Act has no teeth. And, the current Congress is trying to cut back on regulation. It is also extremely unlikely that Congress would pass an enactment adopting the presumption this Comment recommends. More likely, Congress would view such a rule as in the province of the states.
215. Garber, Pharmaceuticals and Medical Devices at 75-76 (cited in note 204).
216. Merton, Exclusion of Pregnant, Pregnable, and Once-Pregnable People at 112-113 (cited in note 59). Litigation is not the only potential solution. There are other ways to effect the needed changes. For example, requiring sponsors to pay for the cost of transpor-
B. A Shifted Burden Success Story

In an effort to eliminate significant health risks posed by toxins created by industry, a similar burden shift was adopted by the state of California in 1986—Proposition 65. Under Proposition 65, the plaintiff in such toxic tort suits need not show injury resulting from non-compliance and need only show that non-compliance took place. The burden then shifts to the defendant manufacturer to show that its practices are safe. The manufacturer must show that its action results in "no significant risk" or "no observable effect." In contrast, in typical environmental tort suits a plaintiff has to show that a substance caused harm in order to succeed in stating a cause of action. In order for a defendant to satisfy its burden under Proposition 65, the company must carry out research to establish safe levels for the chemicals in question.

Proposition 65 motivates companies to find the safest way to use substances in their products. Commentators have found Proposition 65 to be very successful. Many manufacturers have quietly changed formulations rather than risk liability actions. Also, Proposition 65 has succeeded where federal laws have failed. One commentator stated that Proposition 65's secret is simply that it shifts the burden to industry rather than to the innocent public. Placing the knowledge burden on industry can convince it that research on safety levels is in its own best interest. Proposition 65's changed structure has created lower risks and increased public confidence. Thus, the Proposition 65 experience has shown that if companies know that shifting the burden of proof on causation is possible or likely, they may behave differently.

219. Id.
220. Id at 1038.
221. Id.
223. Id. See also Bracing for Big Green, Occupational Hazards 49, 50 (Aug 1990).
225. Id.
226. Id.
227. Id.
V. Conclusion

Both women and society at large are substantially harmed by the practice of excluding fertile women from early phases of clinical trials and of not including sufficient numbers of women in later phases of testing, when it is biologically plausible that women will be affected differently by the drug being studied. The reasons pharmaceutical manufacturers have argued for not including women in the past are mostly based on false assumptions and ignore scientific knowledge. While there will be costs to manufacturers in changing their testing procedures, in weighing researchers' rights with women's rights to safe and effective drugs, and in weighing the high costs of research with equity in society, women and equity should win.

As this Comment describes, however, equity does not mean including large numbers of every subgroup of the population in every clinical trial. Phase 1 subjects must be demographically representative of the targeted market so that they each can have a reasonable impact on the early study. Whether to include large numbers of members of any of the subgroups in later phases should be based on the results of the phase 1 study and on any other existing data, such as animal studies, toxicology studies, and available scientific knowledge of the substances in the drug and their effects in humans.

An injured female plaintiff bringing a failure to test product liability suit, or threatening such a suit, may be the swiftest way to induce pharmaceutical companies to include fertile women in clinical trials of new drugs, and especially in early phases of clinical trials. Shifting the burden of production on the element of causation to the defendant—with a presumption that the defendant failed to study the effects of the drug in women—will facilitate an injured woman's ability to bring one of these suits. Shifting burdens have been successful in similar situations. The legal justifications for shifting burdens and applying presumptions are overwhelmingly met by the situation created when drug companies do not adequately test their drugs on the very same people to whom they market and sell their drugs. This Comment's proposed legal reform would force pharmaceutical companies from their state of inertia to move toward where they should be legally, morally, and scientifically.

228. Note that a further example of the pharmaceutical manufacturers' misguided concerns is the difficulty in proving causation. The manufacturers fear a lawsuit brought by an injured child born to a subject, but do not worry about a lawsuit brought by an injured user of the drug; however, causation is more difficult to prove for a child alleging an injury that was caused at least 21 years prior than for a subject alleging an injury that was caused within a few years of the complaint.